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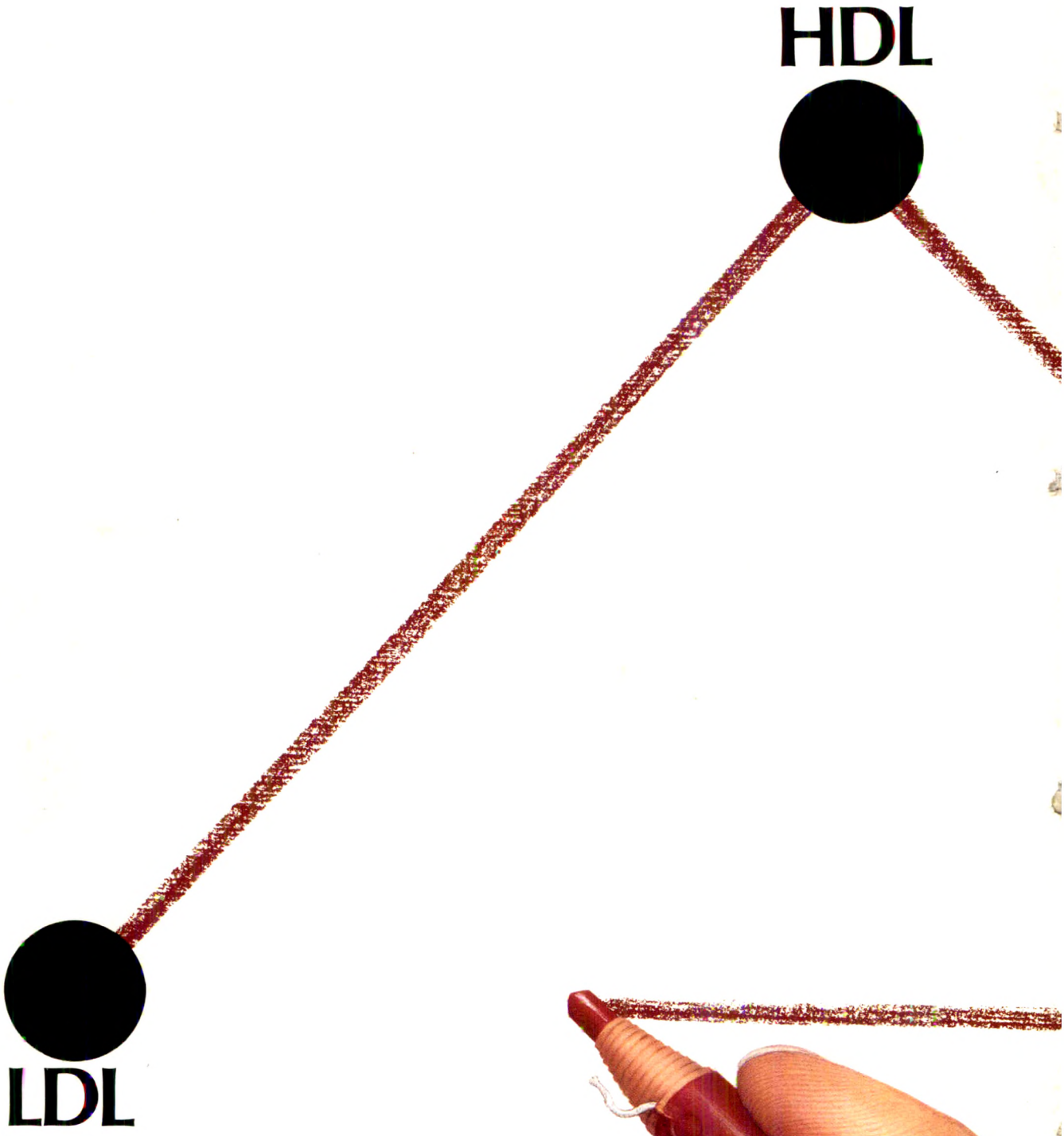
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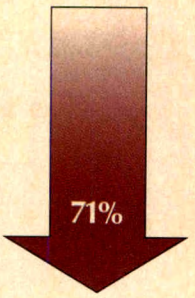


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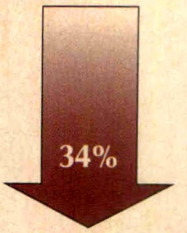
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To reduce heart attack risk, don't overlook coexisting low HDL, high triglycerides, and high LDL. A recently published analysis of data from a Helsinki Heart Study subgroup shows why:

LOPID reduced the incidence of heart attack* 71%



—in a high-risk subgroup of patients with multiple lipid disorders. While the overall reduction in heart attack was 34%, the greatest reduction in heart attack was achieved among those LOPID patients with baseline triglycerides >200 mg/dL and baseline LDL/HDL >5 (n = 154).†[1]



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BID

(gemfibrozil) 600-mg Tablets

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LOPID is indicated for reducing the risk of coronary heart disease in type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.

Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

Reference 1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation.* 1992;85:37-45.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.
†Mean HDL = 35 mg/dL; mean LDL = 208 mg/dL; $P = .005$; 95% CI 21.2 to 118.6.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

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(gemfibrozil) 600-mg Tablets
RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
DRAMATICALLY REDUCES HEART ATTACK

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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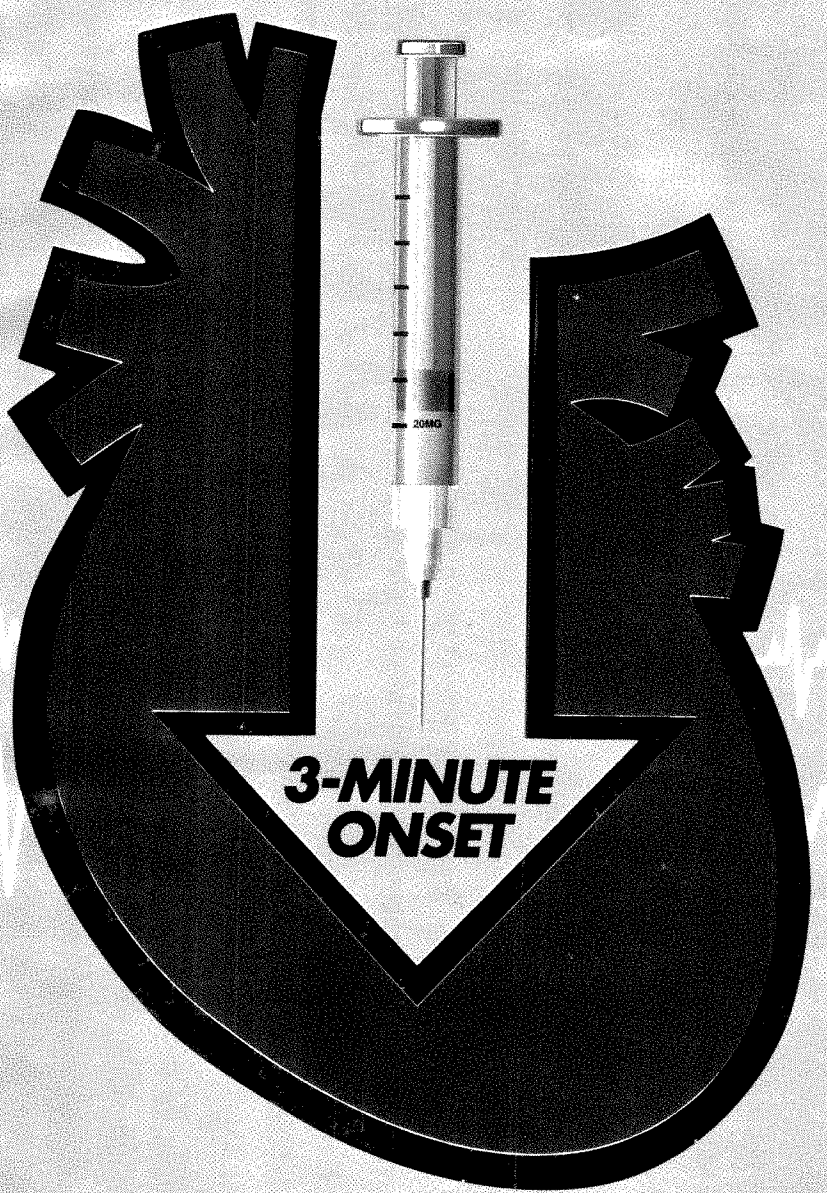
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CIVXE461/A3318

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(diltiazem hydrochloride)

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- 95% response rate within 2 to 7 minutes of administration[1]
- 1- to 3-hour duration of action with initial bolus

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- 3.2 % incidence of symptomatic hypotension[1]*
- 3.9% incidence of injection site reaction[1]
- 1.7% incidence of flushing[1]*
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- Not to be used in patients with WPW and short PR syndrome

Other contraindications: sick sinus syndrome and second- or third-degree AV block, except with a functioning pacemaker; severe hypotension and shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

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*Occurs most often during or immediately following bolus injection.
†Caution should be used in patients with congestive heart failure.

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Please see brief summary of prescribing information on next page.

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CONVENIENT DOSAGE

1	**Beginning treatment as**	**2**	**If response is inadequate, wait 15 minutes**	**3**	**Treatment as**
BOLUS: 0.25 mg/kg actual body weight over 2 minutes		**BOLUS:** 0.35 mg/kg actual body weight over 2 minutes		**INFUSION: 10* to 15 mg/hr** *5 mg/hr may be appropriate starting infusion for some patients.	
20 mg average patient		**25 mg average patient**			

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

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2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

CARDIZEM INJECTABLE...HEART RATE CONTROL THAT IS FAST, SAFE, AND CONTINUOUS

CIVXE461/A3318

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CORONARY ARTERY DISEASE

845
Improved Stenosis Geometry by Quantitative Coronary Arteriography After Vigorous Risk Factor Modification

K. Lance Gould, Dean Ornish, Richard Kirkeeide, Shirley Brown, Yvonne Stuart, Martin Buchi, James Billings, William Armstrong, Thomas Ports, and Larry Scherwitz

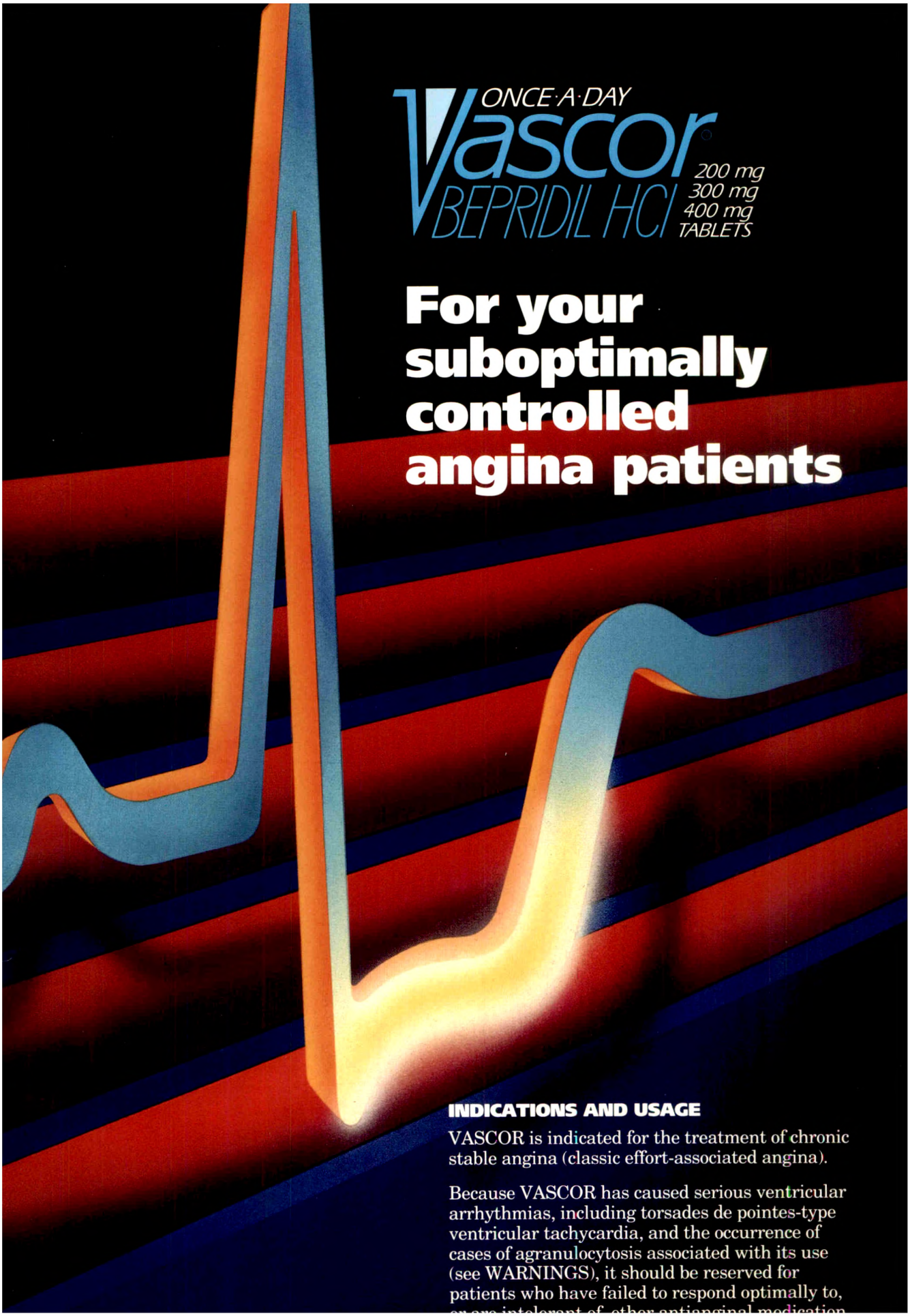
This study is a randomized, controlled, blinded, arteriographic trial to determine effects of a low-cholesterol, low-fat, vegetarian diet, stress management and moderate aerobic exercise on geometric dimensions, shape and fluid dynamic characteristics of coronary artery stenoses in humans. Different stenosis dimensions may change in opposite directions causing stenoses to remold with effects on functional severity not accounted for by percent narrowing. Accordingly, all stenotic dimensions were analyzed, including proximal, minimal and distal diameter, integrated length and exit effects determining stenosis shape, and an integrated measure, stenosis flow reserve, reflecting functional severity. In the control group, complex shape change and stenosis molding characteristic of statistically significant progressing severity occurred with worsening of stenosis flow reserve. In the treated group, complex shape change and stenosis-molding characteristic of significant regressing severity occurred with improved stenosis flow reserve, thereby documenting the multidimensional characteristics of regressing coronary artery disease in humans.

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Thomas H. Marwick, James J. Nemec, Antoine Lafont, Ernesto E. Salcedo, and William J. MacIntyre

The relation between the amount of ischemic and hibernating myocardium, and changes in left ventricular function and exercise capacity after revascularization was examined in 23 patients after infarction. Preoperative myocardial perfusion (using rubidium-82) and fasting postexercise fluoro-18 deoxyglucose (FDG) uptake were assessed by positron emission tomography. Using improvement in an echocardiographic regional wall motion score before and after revascularization to define myocardial viability, the predictive accuracy of a positive FDG "hotspot" was 19 of 26 (73%), with a negative predictive accuracy of 35 of 47 (74%). Patients

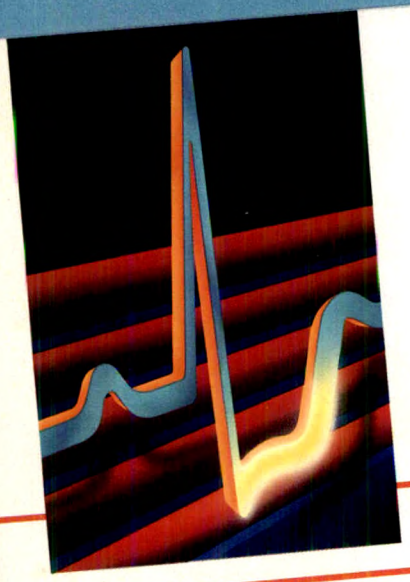
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INDICATIONS AND USAGE

VASCOR is indicated for the treatment of chronic stable angina (classic effort-associated angina).

Because VASCOR has caused serious ventricular arrhythmias, including torsades de pointes-type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to, or are intolerant of, other antianginal medication



Another in a series of case reports

A CASE FOR VASCOR® (bepridil HCl)

James P., 58-year-old building painter*

PRESENTING SYMPTOM: Could not continue to work because of limiting angina

HISTORY: Suboptimal response to a regimen of atenolol, diltiazem, and isosorbide dinitrate; remains uncontrolled despite angioplasty

EXERCISE TOLERANCE TEST:
Total exercise time: 5 min, 1 sec
Time to 1-mm ST depression: 3 min, 12 sec
Time to onset of angina: 2 min, 52 sec

LABORATORY FINDINGS:
Serum potassium: 4.3 mEq/L
ECG: Nonspecific ST abnormality
QTc interval: 406 msec

CLINICAL COURSE: Diltiazem discontinued; VASCOR 200 mg QD initiated, resulting in some improvement after 2 weeks; VASCOR dosage increased to 300 mg QD, resulting in marked improvement after 4 weeks

EXERCISE TOLERANCE TEST:
Total exercise time: 6 min, 1 sec
Time to 1-mm ST depression: 4 min, 12 sec
Time to onset of angina: 4 min, 2 sec
QTc interval range: 440 to 460 msec

FOLLOW-UP: **Over the next 3 months, James P. was able to return to his job part-time and experienced angina only with extreme exertion**

ONCE·A·DAY Vascor® BEPRIDIL HCl 200 mg 300 mg 400 mg TABLETS

*Based on an actual case history submitted by Stephen P. Glasser, MD, Director of the Cardiovascular Unit for Research and Education, University of South Florida Health Science Center

Please see prescribing information.

McNEIL PHARMACEUTICAL

WALLACE LABORATORIES

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V793A 12/17/91

VASCOR®

(bepridil hydrochloride)
Tablets For Oral Administration

INDICATIONS AND USAGE

Chronic Stable Angina (Classic Effort-Associated Angina)

VASCOR (bepridil hydrochloride) is indicated for the treatment of chronic stable angina (classic effort-associated angina). Because VASCOR has caused serious ventricular arrhythmias, including torsades de pointes type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to, or are intolerant of, other anti-anginal medication.

VASCOR may be used alone or in combination with beta blockers and/or nitrates. Controlled clinical studies have shown an added effect when VASCOR is administered to patients already receiving propranolol.

CONTRAINDICATIONS

VASCOR (bepridil hydrochloride) is contraindicated in patients with a known sensitivity to bepridil hydrochloride.

VASCOR is contraindicated in (1) patients with a history of serious ventricular arrhythmias (see WARNINGS–Induction of New Serious Arrhythmias), (2) patients with sick sinus syndrome or patients with second- or third-degree AV block, except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients with uncompensated cardiac insufficiency, (5) patients with congenital QT interval prolongation (see WARNINGS), and (6) patients taking other drugs that prolong QT interval (see PRECAUTIONS-Drug Interactions).

WARNINGS

Induction of New Serious Arrhythmias

VASCOR (bepridil hydrochloride) has Class 1 anti-arrhythmic properties and, like other such drugs, can induce new arrhythmias, including VT/VF. In addition, because of its ability to prolong the QT interval, VASCOR can cause torsades de pointes type ventricular tachycardia. Because of these properties VASCOR should be reserved for patients in whom other anti-anginal agents do not offer a satisfactory effect.

In US clinical trials, the QT and QTc intervals were commonly prolonged by VASCOR in a dose-related fashion. While the mean prolongation of QTc was 8% and of QT was 10%, QTc increases of 25% or more were not uncommon, 5%; 8.7% QT. Increased QT and QTc may be associated with torsades de pointes type VT, which was seen at least briefly, in about 1.0% of patients in US trials; in many cases, however, patients with marked prolongation of QTc were taken off VASCOR therapy. All of the US patients with torsades de pointes had a prolonged QT interval and relatively low serum potassium. French marketing experience has reported over one hundred verified cases of torsades de pointes. While this number based on total use, represents a rate of only 0.01%, the true rate is undoubtedly much higher, as spontaneous reporting systems all suffer from substantial under reporting.

Torsades de pointes is a polymorphic ventricular tachycardia often but not always associated with a prolonged QT interval, and often drug induced. The relation between the degree of QT prolongation and the development of torsades de pointes is not linear and the likelihood of torsades appears to be increased by hypokalemia, use of potassium wasting diuretics, and the presence of antecedent bradycardia. While the safe upper limit of QT is not defined, it is suggested that the interval not be permitted to exceed 0.52 seconds during treatment. If dose reduction does not eliminate the excessive prolongation, VASCOR should be stopped.

Because most domestic and foreign cases of torsades have developed in patients with hypokalemia, usually related to diuretic use or significant liver disease, if concomitant diuretics are needed, low doses and addition or primary use of a potassium sparing diuretic should be considered and serum potassium should be monitored.

VASCOR has been associated with the usual range of pro-arrhythmic effects characteristic of Class 1 anti-arrhythmics (increased premature ventricular contraction rates, new sustained VT, and VT/VF that is more difficult than previously to convert to sinus rhythm). Use in patients with severe arrhythmias (who are most susceptible to certain pro-arrhythmic effects) has been limited, so that risk in these patients is not defined.

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic nonlife-threatening ventricular arrhythmias who had myocardial infarctions more than six days but less than two years previously, an excess mortality/non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The applicability of these results to other populations (e.g., those without recent myocardial infarction) or to other anti-arrhythmic drugs is uncertain, but at present it is prudent to consider any drug documented to provoke new serious arrhythmias or worsening of preexisting arrhythmias as having a similar risk and to avoid their use in the post-infarction period.

Agranulocytosis: In US clinical trials of over 800 patients treated with VASCOR for up to five years, two cases of marked leukopenia and neutropenia were reported. Both patients were diabetic and elderly. One died with overwhelming gram-negative sepsis, itself a possible cause of marked leukopenia. The other patient recovered rapidly when VASCOR was stopped.

Congestive Heart Failure: Congestive heart failure has been observed infrequently (about 1%) during US controlled clinical trials, but experience with the use of VASCOR in patients with significantly impaired ventricular function is limited. There is little information on the effect of concomitant administration of VASCOR and digoxin; therefore, caution should be exercised in treating patients with congestive heart failure.

Hepatic Enzyme Elevation: In US clinical studies with VASCOR in about 1000 patients and subjects, clinically significant (at least 2 times the upper limit of normal) transaminase elevations were observed in approximately 1% of the patients. None of these patients became clinically symptomatic or jaundiced and values returned to normal when the drug was stopped.

Hypokalemia: In clinical trials VASCOR has not been reported to reduce serum potassium levels. Because hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency should be corrected before VASCOR therapy is initiated and normal potassium concentrations should be maintained during VASCOR therapy. Serum potassium should be monitored periodically.

PRECAUTIONS

General

Caution should be exercised when using VASCOR (bepridil hydrochloride) in patients with left bundle branch block or sinus bradycardia (less than 50 b.p.m.). Care should also be exercised in patients with serious hepatic or renal disorders because such patients have not been studied and bepridil is highly metabolized, with metabolites excreted primarily in the urine.

Recent Myocardial Infarction

In US clinical trials with VASCOR, patients with myocardial infarctions within three months prior to initiation of drug treatment were excluded. The initiation of VASCOR therapy in such patients, therefore, cannot be recommended.

Information for Patients

Since QT prolongation is not associated with defined symptomatology, patients should be instructed on the importance of maintaining any potassium supplementation or potassium sparing diuretic, and the need for routine electrocardiograms and periodic monitoring of serum potassium.

The following Patient Information is printed on the carton label of each unit of use bottle of 30 tablets:

As with any medication that you take, you should notify your physician of any changes in your overall condition. Insure that you follow your physician's instructions regarding follow-up visits. Please notify any physician who treats you for a medical condition that you are taking VASCOR® (bepridil hydrochloride), as well as any other medications.

Drug Interactions

Nitrates: The concomitant use of VASCOR with long- and short-acting nitrates has been safely tolerated in patients with stable angina pectoris. Sublingual nitroglycerin may be taken if necessary for the control of acute angina attacks during VASCOR therapy.

Beta-blocking Agents: The concomitant use of VASCOR and beta-blocking agents has been well tolerated in patients with stable angina. Available data are not sufficient, however, to predict the effects of concomitant medication on patients with impaired ventricular function or cardiac conduction abnormalities (see DOSAGE AND ADMINISTRATION).

Digoxin: In controlled studies in healthy volunteers, bepridil hydrochloride either had no effect (one study) or was associated with modest increases, about 30% (two studies) in steady-state serum digoxin concentrations. Limited clinical data in angina patients receiving concomitant bepridil hydrochloride and digoxin therapy indicate no discernible changes in serum digoxin levels. Available data are neither sufficient to rule out possible increases in serum digoxin with concomitant treatment in some patients, nor other possible interactions, particularly in patients with cardiac conduction abnormalities (also see WARNINGS–Congestive Heart Failure).

Oral Hypoglycemics: VASCOR has been safely used in diabetic patients without significantly lowering their blood glucose levels or altering their need for insulin or oral hypoglycemic agents.

General Interactions: Certain drugs could increase the likelihood of potentially serious adverse effects with bepridil hydrochloride. In general, these are drugs that have one or more pharmacologic activities similar to bepridil hydrochloride, including anti-arrhythmic agents such as quinidine and procainamide, cardiac glycosides and tricyclic anti-depressants. Anti-arrhythmics and tricyclic anti-depressants could exaggerate the prolongation of the QT interval observed with bepridil hydrochloride. Cardiac glycosides could exaggerate the depression of AV nodal conduction observed with bepridil hydrochloride.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was revealed in one lifetime study in mice at dosages up to 60 times (for a 60 kg subject) the maximum recommended dosage in man. Unilateral follicular adenomas of the thyroid were observed in a study in rats following lifetime administration of high doses of bepridil hydrochloride, i.e., ≥100 mg/kg/day (20 times the usual recommended dose in man). No mutagenic or other genotoxic potential of bepridil hydrochloride was found in the following standard laboratory tests: the Micronucleus Test for Chromosomal Effects, the Liver Microsome Activated Bacterial Assay for Mutagenicity, the Chinese Hamster Ovary Cell Assay for Mutagenicity, and the Sister Chromatid Exchange Assay. No intrinsic effect on fertility by bepridil hydrochloride was demonstrated in rats.

In monkeys, at 200 mg/kg/day, there was a decrease in testicular weight and spermatogenesis. There were no systematic studies in man related to this point. In rats, at doses up to 300 mg/kg/day, there was no observed alteration of mating behavior nor of reproductive performance.

Usage in Pregnancy

Pregnancy Category C. Reproductive studies (fertility and peri-postnatal) have been conducted in rats. Reduced litter size at birth and decreased pup survival during lactation were observed at maternal dosages 37 times (on a mg/kg basis) the maximum daily recommended therapeutic dosage.

In teratology studies, no effects were observed in rats or rabbits at these same dosages.

There are no well-controlled studies in pregnant women. Use VASCOR in pregnant or nursing women only if the potential benefit justifies the potential risk.

Nursing Mothers

Bepridil is excreted in human milk. Bepridil concentration in human milk is estimated to reach about one third the concentration in serum. Because of the potential for serious adverse reactions in nursing infants from VASCOR a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of VASCOR in children have not been established.

ADVERSE REACTIONS

Adverse reactions were assessed in 529 patients who received VASCOR (bepridil hydrochloride) in controlled trials of 4-12 weeks duration and longer-term uncontrolled studies. The most common side effects occurring more frequently than in control groups were upper gastrointestinal complaints (nausea, dyspepsia or GI distress) in about 22%, diarrhea in about 8%, dizziness in about 15%, asthenia in about 10% and nervousness in about 7%. The adverse reactions seen in at least 2% of bepridil patients in controlled trials are shown in the following list.

Body as a Whole: Asthenia, Headache, Flu Syndrome **Cardiovascular/Respiratory:** Palpitations, Dyspnea, Respiratory Infection **Gastrointestinal:** Dyspepsia, G.I. Distress, Nausea, Dry Mouth, Anorexia, Diarrhea, Abdominal Pain, Constipation **Central Nervous System:** Drowsy, Insomnia, Dizziness, Tremor, Tremor of Hand, Paresthesia **Psychiatric:** Nervous **Special Senses:** Tinnitus.

About 15% of patients however, left bepridil treatment because of adverse experiences. In controlled clinical trials, these were principally gastrointestinal (1.0%), dizziness (1.0%), ventricular arrhythmias (1.0%) and syncope (0.6%).

Across all controlled and uncontrolled trials, VASCOR was evaluated in over 800 patients with chronic angina. In addition to the adverse reactions noted above, the following were observed in 0.5 to 2.0% of the VASCOR patients or are rarer, but potentially important events seen in clinical studies or reported in post marketing experience. In most cases it is not possible to determine whether there is a causal relationship to bepridil treatment.

Body as a Whole: Fever, pain, myalgic asthenia, superinfection, flu syndrome. **Cardiovascular/Respiratory:** Sinus tachycardia, sinus bradycardia, hypertension vasodilation, edema, ventricular premature contractions, ventricular tachycardia, prolonged QT interval, rhinitis, cough, pharyngitis. **Gastrointestinal:** Flatulence, gastritis, appetite increase, dry mouth, constipation. **Musculoskeletal:** Arthritis. **Central Nervous System:** Fainting, vertigo, akathisia, drowsiness, insomnia, tremor. **Psychiatric:** Depression, anxiousness, adverse behavior effect. **Skin:** Rash, sweating, skin irritation. **Special Senses:** Blurred vision, tinnitus, taste change. **Urogenital:** Loss of libido, impotence. **Abnormal Lab Values:** Abnormal liver function test, SGPT increase.

Certain cardiovascular events, such as acute myocardial infarction (about 3% of patients) worsened heart failure (1.9%), worsened angina (4.5%), severe arrhythmia (about 2.4% VT/VF) and sudden death (1.6%) have occurred in patients receiving bepridil, but have not been included as adverse events because they appear to be, and cannot be distinguished from, manifestations of the patient's underlying cardiac disease. Such events as torsades de pointes arrhythmias, prolonged QT/QTc, bradycardia, first degree heart block, which are probably related to bepridil, are included in the tables.

OVERDOSAGE

In the event of overdosage, we recommend close observation in a cardiac care facility for a minimum of 48 hours and use of appropriate supportive measures in addition to gastric lavage. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase transmembrane calcium ion influx. Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Ventricular tachycardia should be handled by cardioversion and, if persistent, by overdrive pacing. There has been one experience with overdosage in which a patient inadvertently took a single dose of 1600 mg of VASCOR (bepridil hydrochloride). The patient was observed for 72 hours in intensive care, but no significant adverse experiences were noted.

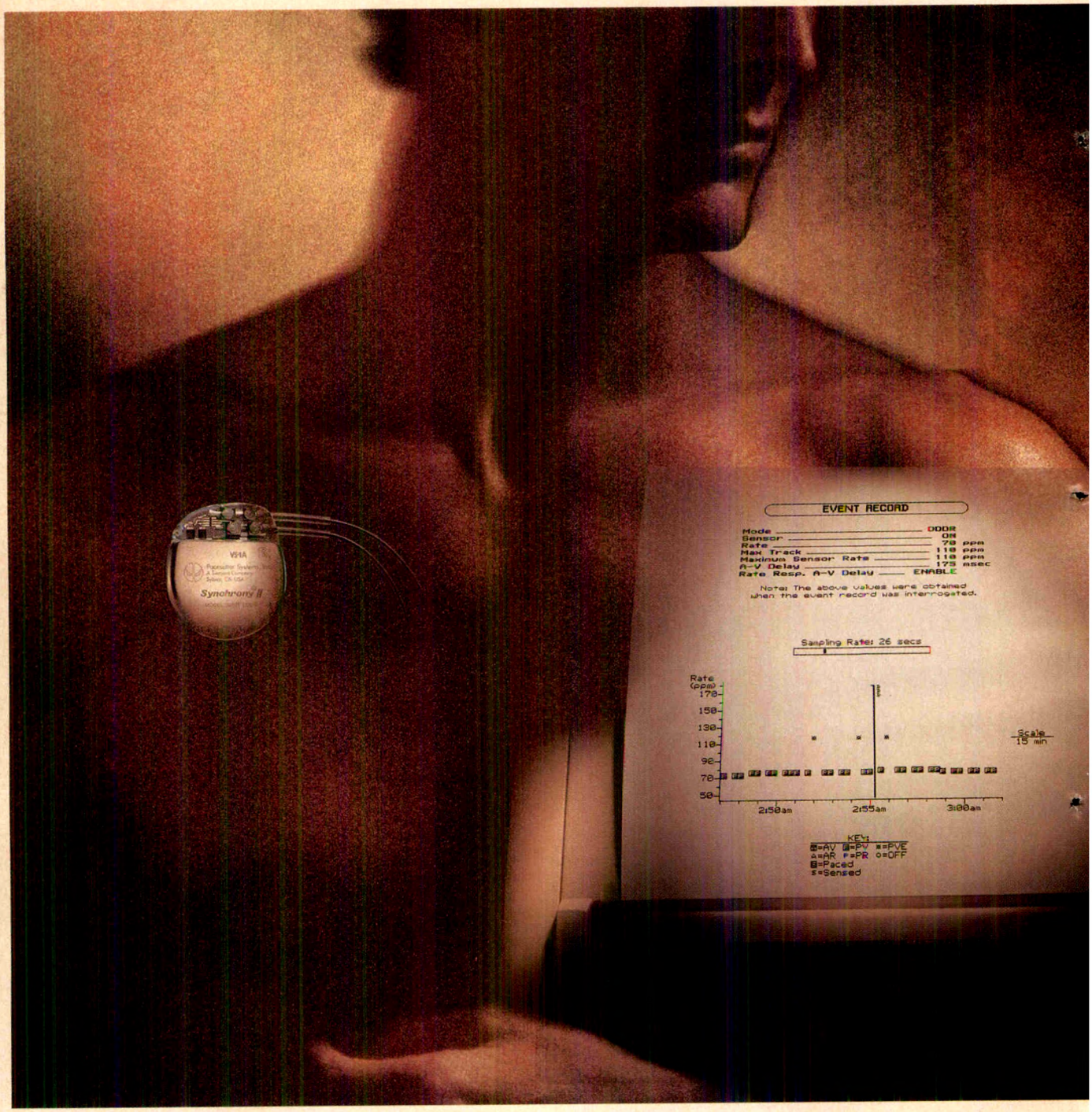
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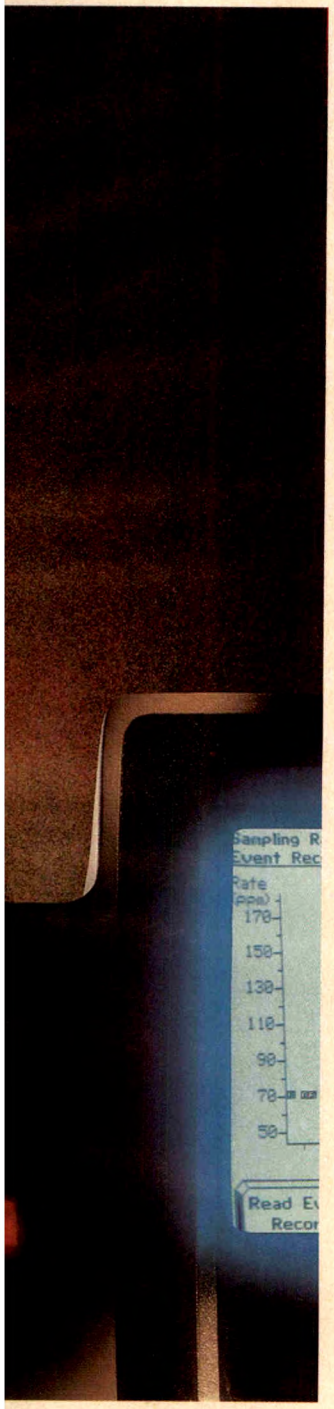
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with increased FDG uptake in >2 segments had improvements in exercise parameters and mean left ventricular wall motion index.

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Implications of Inferior ST-Segment Elevation Accompanying Anterior Wall Acute Myocardial Infarction for the Angiographic Morphology of the Left Anterior Descending Coronary Artery Morphology and Site of Occlusion

Peter M. Sapin, David R. Musselman, Gregory J. Dehmer, and Wayne E. Cascio

Little is known concerning reciprocal inferior ST-segment elevation (sum of ST-segment elevation in leads II, III and aVF ≥3 mm) accompanying anterior acute myocardial infarction (AMI). Of 42 consecutive patients undergoing cardiac catheterization after anterior AMI, inferior ST-segment elevation was found in 7 (16%). In 5 of the 7 patients, there was an occlusion beyond 3 major branches in a "wrap around" left anterior descending coronary artery. This morphology was seen in only 2 of the other 35 patients ($p < 0.001$). It is postulated that significant inferior ST elevation during anterior AMI results from 2 necessary conditions: (1) inferior transmural ischemia (i.e., wrap around left anterior descending coronary artery) and (2) less reciprocal ST depression due to a smaller mass of ischemic anterior wall myocardium (i.e., distal occlusion).

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Influence of Thrombolysis on Signal-Averaged Electrocardiogram and Late Arrhythmic Events After Acute Myocardial Infarction

Roberto Pedretti, Antonio Laporta, Mario D. Etro, Adelia Gementi, Roberto Bonelli, Claudio Anzà, Enrica Colombo, Franco Maslowsky, Francesco Santoro, and Bruno Carù

The influence of intravenous thrombolysis on both prevalence of ventricular late potentials and incidence of late arrhythmic events was evaluated in 174 consecutive patients surviving a first myocardial infarction. The rate of late potentials was significantly lower in both the group treated with thrombolysis and that with a patent infarct-related artery on coronary arteriography. Conversely, mean left ventricular ejection fraction was not significantly different. Therefore, thrombolysis and patency of the infarct-related artery reduced prevalence of late potentials independently of global left ventricular function. Late potentials are independent markers of malignant ventricular tachyarrhythmias; the lower prevalence of late potentials after thrombolysis suggests improved ventricular electrical stability. The prevention of an arrhythmogenic substrate development could have an important role in increasing survival after thrombolysis.

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Cardiopulmonary Receptor and Arterial Baroreceptor Reflexes After Acute Myocardial Infarction

Guido Grassi, Cristina Giannattasio, Gino Seravalle, Giuseppe Osculati, Franco Valagussa, Alberto Zanchetti, and Giuseppe Mancia

Impaired baroreflex–heart rate control observed 2 days after a myocardial infarction was reported to have undergone an improvement 10 days after

Continued on page A24

The word for all the benefits of Activase® (Alteplase, recombinant)

Patency: opens arteries early to save lives in AMI

Safety: clinically documented low incidence of intracranial bleeding (ICB) even when used with IV heparin

Survival: opens arteries and saves lives when used within 5 hours of AMI onset

Bleeding is the most common complication of thrombolytic therapy, with intracranial bleeding being the most serious. Activase® is contraindicated in patients with: active internal bleeding, history of cerebrovascular accident, recent (within two months) intracranial or intraspinal surgery or trauma, intracranial neoplasm, arteriovenous malformation, or aneurysm, known bleeding diathesis, severe uncontrolled hypertension. (See WARNINGS section of prescribing information.)

Please see brief summary of prescribing information on the last page of this advertisement.

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Please see brief summary of prescribing information on following page.

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A TISSUE PLASMINOGEN ACTIVATOR

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ACTIVASE®
ALTEPLASE, RECOMBINANT
A TISSUE PLASMINOGEN ACTIVATOR

Brief Summary
Consult full prescribing information before using.

INDICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial infarction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct size, the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms.

ACTIVASE® is also indicated in the management of acute massive pulmonary embolism (PE) in adults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or multiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable hemodynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis should be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such as lung scanning.

CONTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension.

WARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes occurred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy was continuing.

As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites of catheter insertion, arterial and venous puncture, cutdown and needle puncture).

Intramuscular injections and nonessential handling of the patient should be avoided during treatment with ACTIVASE® Venipunctures should be performed carefully and only as required.

Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an upper extremity vessel accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding.

Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and any concomitant heparin should be terminated immediately.

Each patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

In the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed against the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass graft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovascular disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 days) trauma • Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg • High likelihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • Subacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or renal disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other hemorrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously infected site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • Any other condition in which bleeding constitutes a significant hazard or would be particularly difficult to manage because of its location.

Arrhythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia and/or ventricular irritability be available when infusions of ACTIVASE® are administered.

Pulmonary Embolism It should be recognized that the treatment of pulmonary embolism with ACTIVASE®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying deep vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying deep venous thrombi should be considered.

PRECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism should be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial puncture must be avoided. Arterial and venous punctures should be minimized. In the event of serious bleeding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be reversed by protamine.

Readministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction occurs, infusion should be discontinued immediately and appropriate therapy initiated.

Although sustained antibody formation in patients receiving one dose of ACTIVASE® has not been documented, readministration should be undertaken with caution.

Laboratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. ACTIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active under *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some extent mitigate this phenomenon.

Drug Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, during or after ACTIVASE® therapy.

Use of Anticoagulants Heparin has been administered concomitantly with and following infusions of ACTIVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

Pregnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is also not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if clearly needed.

Pediatric Use Safety and effectiveness of ACTIVASE® in children has not been established.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which evaluated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.

Studies to determine mutagenicity (Ames test) and chromosomal aberration assays in human lymphocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease in mitotic index, was evidenced only after prolonged exposure and only at the highest concentrations tested.

Nursing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a nursing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not signficantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE® is for intravenous administration only. **ACUTE MYOCARDIAL INFARCTION: Administer ACTIVASE® as soon as possible after the onset of symptoms.**

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the ACTIVASE® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

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ACTIVASE®, Alteplase, recombinant
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the acute coronary event. This study examines whether (1) this improvement means a "normalization" of baroreflex sensitivity, and (2) the cardiopulmonary reflex is affected by myocardial infarction. In 30 patients examined 8 to 11 days after an anterior or inferior myocardial infarction, baroreceptor–heart rate reflex sensitivity (neck chamber technique) was superimposable to that observed in age-matched controls (-6.2 ± 0.8 vs -6.0 ± 0.6 ms/mm Hg, mean $\pm$ SEM) and was unchanged when reexamined 10 days later. In contrast, the ability of cardiopulmonary receptors to modulate forearm vasoconstrictor tone during changes in central venous pressure (lower body suction and passive leg raising techniques) was markedly impaired in 12 patients studied 8 to 11 days after myocardial infarction compared with that in control subjects. This impairment, however, virtually disappeared when patients were reexamined 28 to 45 days later. Thus baroreflex–heart rate control is virtually normal 10 days after myocardial infarction, while cardiopulmonary reflex is impaired. However, this impairment is also transient in nature.

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An Indian Experiment with Nutritional Modulation in Acute Myocardial Infarction

Ram B. Singh, Shanti S. Rastogi, Rakesh Verma, Laxmi Bolaki, and Reema Singh

In a randomized, 6-week intervention trial, 206 patients with suspected acute myocardial infarction were administered a low-caloric diet rich in fruits, vegetables, cereals and nuts, and 202 were on the usual diet. Clinical and laboratory data at entry to the study were comparable. Dietary adherence was checked by a questionnaire. Group A received a significantly low-caloric, high-polyunsaturated/saturated fat diet compared with that of group B (higher saturated fat and cholesterol). Group A had a significant decrease in serum total and low-density lipoprotein cholesterols, and triglycerides, with no decrease in high-density lipoprotein cholesterol. Group A also had a significantly greater decrease in mean body weight than did group B. After 6 weeks, there was a significant decrease (34.5%) in total cardiac end points including nonfatal (17 vs 25) and fatal (8 vs 12) myocardial infarction, and sudden cardiac death (29 vs 44; $p < 0.01$) in group A compared with those in group B. There was no significant decrease in total mortality (including cardiac mortality) in group A compared with that in group B (12 vs 21) owing to the small number of events.

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Early Hemodynamic Results of Left Ventricular Reconstructive Surgery for Anterior Wall Left Ventricular Aneurysm

Marisa Di Donato, Giuseppe Barletta, Mauro Maioli, Fabio Fantini, Philippe Coste, Michel Sabatier, Francoise Montiglio, and Vincent Dor

To assess the efficacy of left ventricular (LV) reconstruction after aneurysmectomy on LV function, 35 consecutive patients with anterior LV aneurysm were analyzed. Coronary revascularization was performed concurrently. Global perioperative mortality was 4.8%. Postintervention LV volumes and filling pressure significantly decreased, and ejection fraction significantly increased. Regional LV wall motion improved in all, but the anterobasal region and the extent of asynergy significantly decreased. Six

Continued on page A26

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of the 35 patients had a deterioration of postintervention ejection fraction; they had no reduction in LV volumes and no improvement in wall kinetics. No significant differences were found in parameters before intervention among patients.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Correlations Among Time and Frequency Domain Measures of Heart Period Variability Two Weeks After Acute Myocardial Infarction

J. Thomas Bigger, Jr., Joseph L. Fleiss, Richard C. Steinman, Linda M. Rolnitzky, Robert E. Kleiger, and Jeffrey N. Rottman

Seven hundred fifteen participants from a multicenter natural history study of acute myocardial infarction were studied to determine the correlations among time and frequency domain measures of heart period variability and the predictive value of time domain measures for death during follow-up. Each of 4 bands in the heart period power spectrum had 1 or 2 corresponding variables in the time domain that correlated with it so strongly ($r \geq 0.90$) that the variables were essentially equivalent. Time domain measures of heart period variability, especially those that measure ultra low or low-frequency power, are strongly and independently associated with death during follow-up.

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Survival After Implantation of the Cardioverter Defibrillator

David Newman, Mary Jane Sauve, John Herre, Jonathan J. Langberg, Michael A. Lee, Christina Titus, Jay Franklin, Melvin M. Scheinman, and Jerry C. Griffin

The actuarial survival of 60 implantable cardioverter defibrillator (ICD) recipients was compared with that of 120 controls. Controls were matched to ICD patients according to age, ejection fraction, amiodarone use, presenting arrhythmia and heart disease. There were 13 deaths in the ICD group and 59 control deaths during a mean follow-up of 23.5 months for controls and 18.5 months for ICD patients ($p < 0.05$).

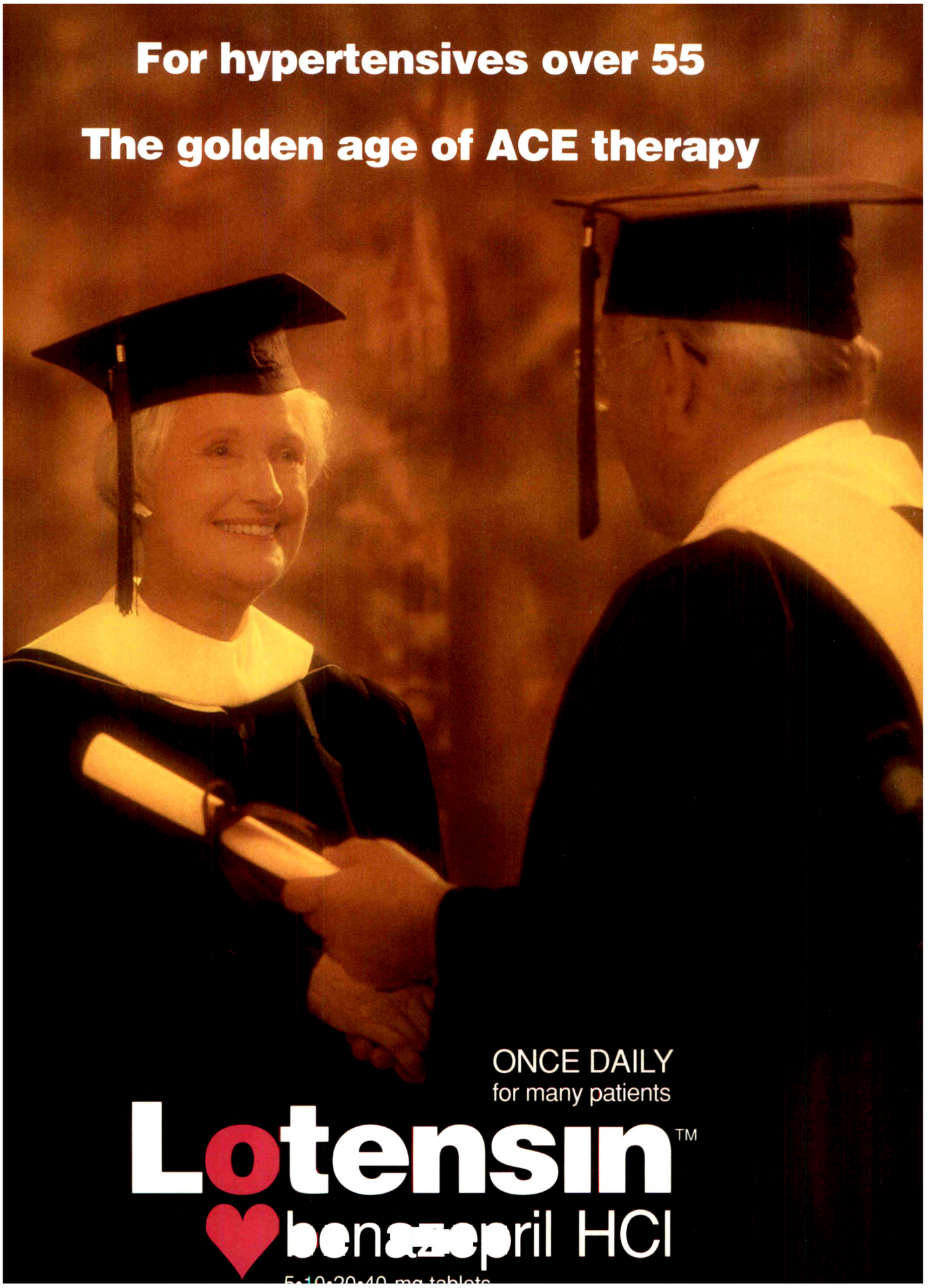
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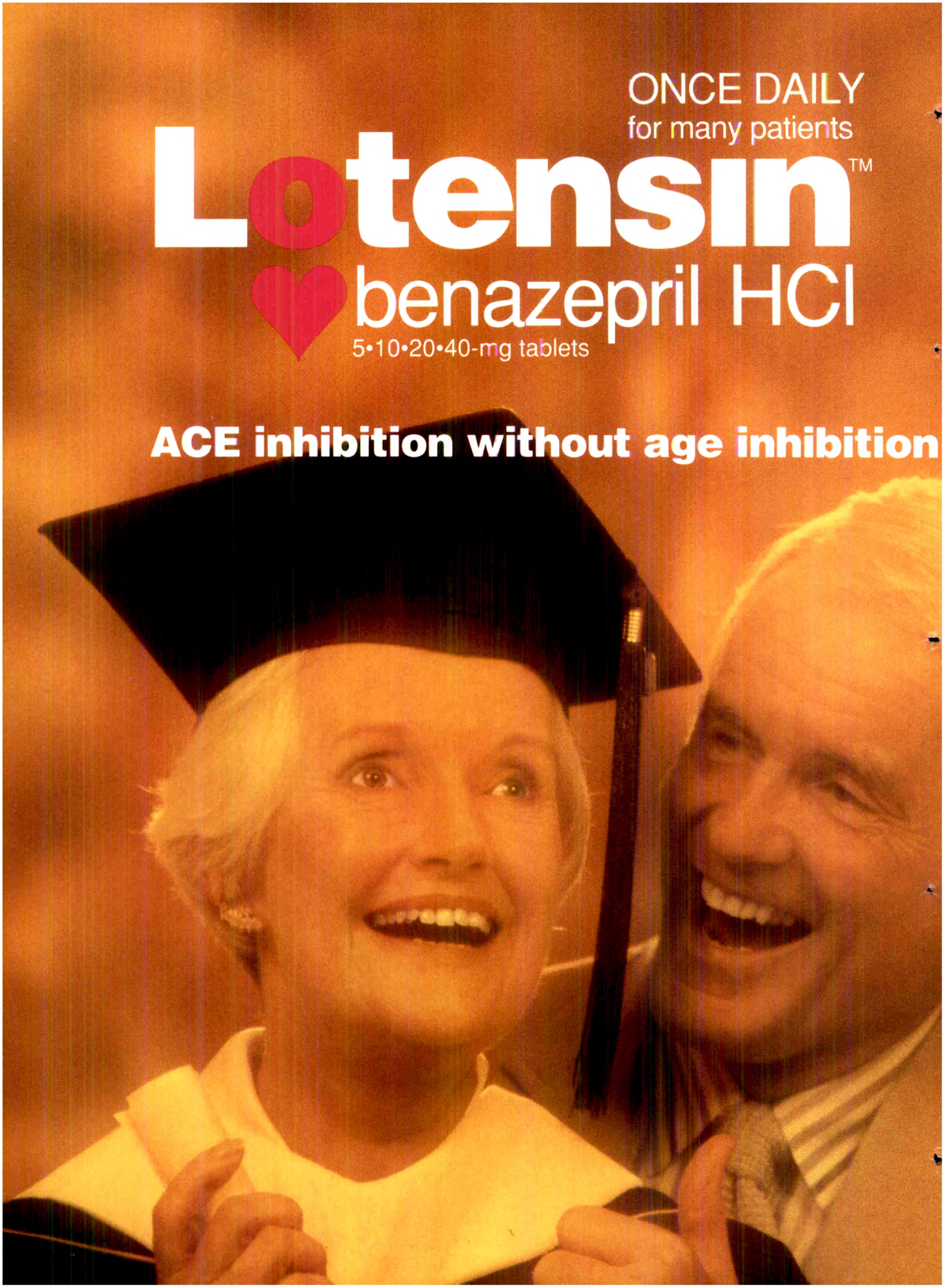
Head-Upright Tilt-Table Testing in Evaluation and Management of the Malignant Vasovagal Syndrome

Blair P. Grubb, Peter Temesy-Armos, Joseph Moore, Douglas Wolfe, Harry Hahn, and Laura Elliot

Vasovagally mediated cardiac asystole has been proposed as a potential cause of sudden cardiac death. To assess this possibility and identify characteristics that define this group with vasovagally mediated asystole, head-upright tilt-table testing was performed in 50 consecutive patients (26 women and 24 men, mean age 42 ± 10 years) with recurrent unexplained syncope. The upright tilt-table test was performed in the fasting state for 30 minutes, with or without the use of intravenous isoproterenol (1 to 3 μg/min). Reproducible tilt-induced asystole occurred in 10 pa-

Continued on page A32


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- propranolol[3]
- furosemide[6]
- warfarin[5]
- cimetidine[3]
- chlorthalidone[3]
- naproxen[3]
- atenolol[3]
- hydrochlorothiazide[7]

The evaluation of any hypertensive patient should include renal function studies. ACE inhibition may cause changes in renal function in susceptible individuals. Lotensin is contraindicated in patients who are hypersensitive to this product or to any other ACE inhibitor. Angioedema has been reported in patients receiving ACE inhibitors. Please consult brief summary of Prescribing Information, including the "Drug Interactions and Precautions - Impaired Renal Function" sections on last page.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE Lotensin is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using Lotensin, consideration should be given to the fact that another angiotensin-converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that Lotensin does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS Lotensin is contraindicated in patients who are hypersensitive to this product or to any other ACE inhibitor.

WARNINGS-Angioedema Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin-converting enzyme inhibitors. In U.S. clinical trials, symptoms consistent with angioedema were seen in none of the subjects who received placebo and in about 0.5% of the subjects who received Lotensin. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine injection 1:1000 (0.3 mL to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).**

Hypotension Lotensin can cause symptomatic hypotension. Like other ACE inhibitors, benazepril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and/or salt-depletion should be corrected before initiating therapy with Lotensin.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, Lotensin therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of benazepril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position, and, if necessary, treated with intravenous infusion of physiological saline. Lotensin treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis Another angiotensin-converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of benazepril are insufficient to show that benazepril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of neonatal hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial malformations, hypoplastic lung development, and intrauterine growth retardation. Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease.

It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hypokalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Benazepril could theoretically be removed from the neonatal circulation by exchange transfusion, but no experience with this procedure has been reported.

At doses that did not induce maternal toxicity, no embryotoxic, fetotoxic or teratogenic effects of Lotensin were seen in studies of pregnant rats, mice, and rabbits. On a mg/m^2 basis, the doses used in these studies were 60 times (in rats), 9 times (in mice), and more than 0.8 times (in rabbits) the maximum recommended human dose (assuming a 50 kg woman). On a mg/kg basis these multiples are 300 times (in rats), 90 times (in mice) and more than 3 times (in rabbits) the maximum recommended human dose.

PRECAUTIONS-General ***Impaired Renal Function:*** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors, including Lotensin, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In a small study of hypertensive patients with renal artery stenosis in a solitary kidney or bilateral renal artery stenosis, treatment with Lotensin was associated with increases in blood urea nitrogen and serum creatinine; these increases were reversible upon discontinuation of Lotensin or diuretic therapy, or both. When such patients are treated with ACE inhibitors, renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when Lotensin has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction of Lotensin and/or discontinuation of the diuretic may be required. **Evaluation of the hypertensive patient should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).** ***Hyperkalemia:*** In clinical trials, hyperkalemia (serum potassium at least 0.5 mEq/L greater than the upper limit of normal) occurred in approximately 1% of hypertensive patients receiving Lotensin. In most cases, these were isolated values which resolved despite continued therapy. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with Lotensin (see Drug Interactions). ***Impaired Liver Function:*** In patients with hepatic dysfunction due to cirrhosis, levels of benazeprilat are essentially unaltered. ***Surgery/Anesthesia:*** In patients undergoing surgery or during anesthesia with agents that produce hypotension, benazepril will block the angiotensin II formation that could otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients ***-Angioedema:*** Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, or tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician. ***Symptomatic Hypotension:*** Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported to the prescribing physician. Patients should be told that if syncope occurs, Lotensin should be discontinued until the prescribing physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope. ***Hyperkalemia:*** Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician. ***Neutropenia:*** Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Drug Interactions ***-Diuretics:*** Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with Lotensin. The possibility of hypotensive effects with Lotensin can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with Lotensin. If this is not possible, the starting dose should be reduced (see DOSAGE AND ADMINISTRATION). ***Potassium Supplements and Potassium-Sparing Diuretics:*** Lotensin can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently. ***Oral Anticoagulants:*** Interaction studies with warfarin and acenocoumarol failed to identify any clinically important effects on the serum concentrations or clinical effects of these anticoagulants. ***Lithium:*** Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased. ***Other:*** No clinically important pharmacokinetic interactions occurred when Lotensin was administered concomitantly with hydrochlorothiazide, chlorthalidone, furosemide, digoxin, propranolol, atenolol, naproxen, or cimetidine.

Lotensin has been used concomitantly with beta-adrenergic-blocking agents, calcium-channel-blocking agents, diuretics, digoxin, and hydralazine, without evidence of clinically important adverse interactions. Benazepril, like other ACE inhibitors, has had less than additive effects with beta-adrenergic blockers, presumably because both drugs lower blood pressure by inhibiting parts of the renin-angiotensin system.

Carcinogenesis, Mutagenesis, Impairment of Fertility No evidence of carcinogenicity was found when benazepril was administered by gavage to rats and mice for up to two years at doses of up to 150 mg/kg/day. When compared on the basis of body weights, this dose is 110 times the maximum recommended human dose. When compared on the basis of body surface areas, this dose is 18 and 9 times (rats and mice, respectively) the maximum recommended human dose (calculations assume a patient weight of 60 kg). No mutagenic activity was detected in the Ames test in bacteria (with or without metabolic activation), in an in vitro test for forward mutations in cultured mammalian cells, or in a nucleus anomaly test. In doses of 50-500 mg/kg/day (6-60 times the maximum recommended human dose based on mg/m^2 comparison and 37-375 times the maximum recommended human dose based on a mg/kg comparison), Lotensin had no adverse effect on the reproductive performance of male and female rats.

Pregnancy Category D See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers Minimal amounts of unchanged benazepril and of benazeprilat are excreted into the breast milk of lactating women treated with benazepril. A newborn child ingesting entirely breast milk would receive less than 0.1% of the mg/kg maternal dose of benazepril and benazeprilat.

Geriatric Use Of the total number of patients who received benazepril in U.S. clinical studies of Lotensin, 18% were 65 or older while 2% were 75 or older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS Lotensin has been evaluated for safety in over 6000 patients with hypertension; over 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was comparable in Lotensin and placebo patients.

The reported side effects were generally mild and transient, and there was no relation between side effects and age, duration of therapy, or total dosage within the range of 2 to 80 mg. Discontinuation of therapy because of a side effect was required in approximately 5% of U.S. patients treated with Lotensin and in 3% of patients treated with placebo.

The most common reasons for discontinuation were headache (0.6%) and cough (0.5%).

In placebo-controlled trials, cough was reported by 68 of 2004 benazepril-treated patients (3.4%) and by 7 of 525 placebo-treated patients (1.3%). This was the only adverse effect with incidence at least 1% that was significantly more frequent in benazepril-treated patients than in patients treated with placebo.

The side effects considered possibly or probably related to study drug that occurred in U.S. controlled trials in more than 1% of patients treated with Lotensin are shown below.

PATIENTS IN U.S. PLACEBO-CONTROLLED STUDIES

	LOTENSIN (N = 1629)		PLACEBO (N = 498)	
	N	%	N	%
Headache	82	5.0	21	4.2
Dizziness	53	3.3	12	2.4
Fatigue	42	2.6	11	2.2
Cough	31	1.9	5	1.0
Nausea	23	1.4	5	1.0

Other adverse experiences reported in controlled clinical trials (in less than 1% of benazepril patients), and rarer events seen in postmarketing experience, include the following (in some, a causal relationship to drug use is uncertain): ***Cardiovascular:*** Symptomatic hypotension was seen in 0.3% of patients, postural hypotension in 0.4%, and syncope in 0.1%; these reactions led to discontinuation of therapy in 4 patients who had received benazepril monotherapy and in 9 patients who had received benazepril with hydrochlorothiazide (see PRECAUTIONS and WARNINGS). Other reports included angina pectoris, palpitations, and peripheral edema. ***Renal:*** Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine. ***Angioedema:*** Angioedema has been reported in patients receiving ACE inhibitors. During clinical trials in hypertensive patients with benazepril, 0.5% of patients experienced edema of the lips or face without other manifestations of angioedema. Angioedema associated with laryngeal edema and/or shock may be fatal. If angioedema of the face, extremities, lips, tongue, or glottis and/or larynx occurs, treatment with Lotensin should be discontinued and appropriate therapy instituted immediately (see WARNINGS). ***Gastrointestinal:*** Constipation, gastritis, vomiting, and melena. ***Dermatologic:*** Apparent hypersensitivity reactions (manifested by dermatitis, pruritis, or rash) and flushing. ***Neurologic and Psychiatric:*** Anxiety, decreased libido, hypertonia, insomnia, nervousness, and paresthesia. ***Other:*** Arthralgia, arthritis, asthenia, asthma, bronchitis, dyspnea, impotence, infection, myalgia, sinusitis, sweating, and urinary tract infection.

Clinical Laboratory Test Findings

Creatinine and Blood Urea Nitrogen: Of hypertensive patients with no apparent preexisting renal disease, about 2% have sustained increases in serum creatinine to at least 150% of their baseline values while receiving Lotensin, but most of these increases have disappeared despite continuing treatment. A much smaller fraction of these patients (less than 0.1%) developed simultaneous (usually transient) increases in blood urea nitrogen and serum creatinine. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis (see PRECAUTIONS, General).

Potassium: Since benazepril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently (see PRECAUTIONS). ***Hemoglobin:*** Decreases in hemoglobin (a low value and a decrease of 5 g/dL) were rare, occurring in only 1 of 2014 patients receiving Lotensin alone and in 1 of 1357 patients receiving Lotensin plus a diuretic. No U.S. patients discontinued treatment because of decreases in hemoglobin. ***Other (causal relationships***

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unknown): Clinically important changes in standard laboratory tests were rarely associated with Lotensin administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of hyponatremia, electrocardiographic changes, leukopenia, eosinophilia, and proteinuria. In U.S. trials, less than 0.5% of patients discontinued treatment because of laboratory abnormalities.

OVERDOSAGE Single oral doses of 3 g/kg benazepril were associated with significant lethality in mice. Rats however, tolerated single oral doses of up to 6 g/kg. Reduced activity was seen at 1 g/kg in mice and at 5 g/kg in rats. Human overdoses of benazepril have not been reported, but the most common manifestation of human benazepril overdosage is likely to be hypotension.

Laboratory determinations of serum levels of benazepril and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of benazepril overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of benazepril and its metabolites. Benazeprilat can be removed from the body by dialysis, but this intervention should rarely, if ever, be required.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of benazepril overdose, but angiotensin II is essentially unavailable outside of scattered research facilities. Because the hypotensive effect of benazepril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat benazepril overdose by infusion of normal saline solution.

DOSAGE AND ADMINISTRATION The recommended initial dose for patients not receiving a diuretic is 10 mg once-a-day. The usual maintenance dosage range is 20-40 mg per day administered as a single dose or in two equally divided doses. A dose of 80 mg gives an increased response, but experience with this dose is limited. The divided regimen was more effective in controlling trough (pre-dosing) blood pressure than the same dose given as a once-daily regimen. Dosage adjustment should be based on measurement of peak (2-6 hours after dosing) and trough responses. If a once-daily regimen does not give adequate trough response an increase in dosage or divided administration should be considered. If blood pressure is not controlled with Lotensin alone, a diuretic can be added.

Total daily doses above 80 mg have not been evaluated.

Concomitant administration of Lotensin with potassium supplements, potassium salt substitutes, or potassium-sparing diuretics can lead to increases of serum potassium (see PRECAUTIONS).

In patients who are currently being treated with a diuretic, symptomatic hypotension occasionally can occur following the initial dose of Lotensin. To reduce the likelihood of hypotension, the diuretic should, if possible, be discontinued two to three days prior to beginning therapy with Lotensin (see WARNINGS). Then, if blood pressure is not controlled with Lotensin alone, diuretic therapy should be resumed.

If the diuretic cannot be discontinued, an initial dose of 5 mg Lotensin should be used to avoid excessive hypotension.

Dosage Adjustment in Renal Impairment

For patients with a creatinine clearance <30 mL/min/1.73 m^2 (serum creatinine >3 mg/dL), the recommended initial dose is 5 mg Lotensin once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 40 mg.

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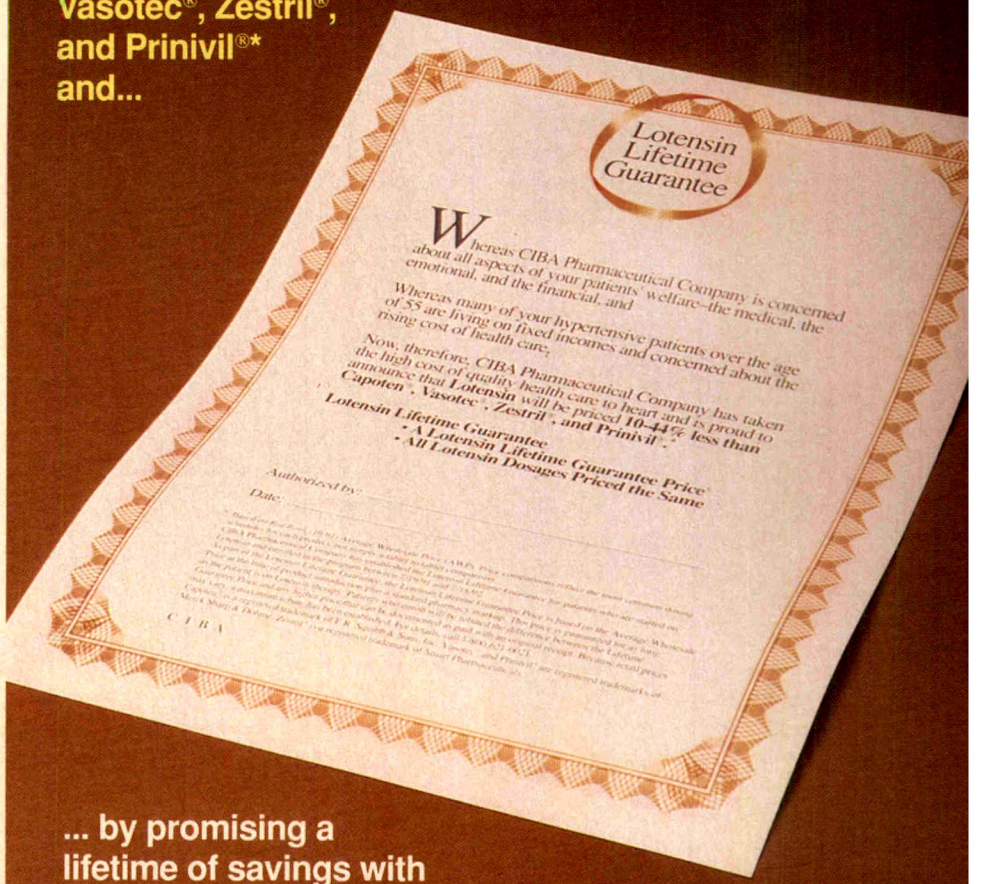
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tients (7 men and 3 women, mean age 23 ± 12 years) (7 patients during the baseline tilt, and 3 during isoproterenol infusion). Analysis of this group revealed that they had significantly more frequent and severe syncopal episodes than did those patients with tilt-induced syncope without asystole. All patients who had tilt-induced asystole eventually became tilt-table negative with therapy (4 with β blockers, 2 with disopyramide, and 4 with atrioventricular permanent pacing), and over a mean follow-up of 21 ± 6 months no further syncopal episodes occurred. It is concluded that patients with recurrent tilt-induced asystole represent a distinct subgroup that has recurrent severe syncope that may mimic or result in sudden cardiac death. Head-upright tilt-table testing is clinically useful in the diagnosis of this malignant vasovagal syndrome and in the evaluation of prophylactic therapy.

909

Usefulness of Predischarge Electrophysiologic Study in Predicting Late Outcome After Surgical Ablation of the Accessory Pathway in the Wolff-Parkinson-White Syndrome

San-Jou Yeh, Chun-Chieh Wang, Fun-Chung Lin, Jen-Ping Chang, Chau-Hsiung Chang, and Delon Wu

A predischarge electrophysiologic study was performed in 113 patients with the Wolff-Parkinson-White syndrome undergoing surgical ablation of the accessory pathway. The predischarge study showed presence of ventricular preexcitation with intact retrograde accessory pathway conduction in 4 patients, and induction of supraventricular tachycardia in 4. Recurrence of supraventricular tachycardia occurred in 5 patients during follow-up of 28 ± 26 months. Of these 5 patients, 2 had inducible and 3 had no inducible tachycardia during the predischarge study. The overall predictive accuracy, and negative and positive predictive values of the predischarge study in predicting late recurrence of ventricular preexcitation or tachycardia were 95, 96 and 67%, respectively.

SYSTEMIC HYPERTENSION

913

Significance of Ventricular Arrhythmias in Systemic Hypertension with Left Ventricular Hypertrophy

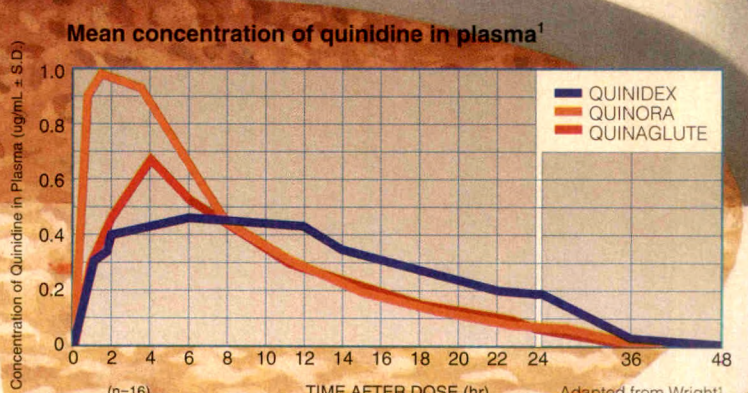
Stuart D. Pringle, Francis G. Dunn, Peter W. Macfarlane, James H. McKillop, A. Ross Lorimer, and Stuart M. Cobbe

The prevalence and significance of ventricular arrhythmias were studied in 90 hypertensive patients with left ventricular hypertrophy by undertaking 48-hour ambulatory electrocardiographic (ECG) monitoring, ECG signal-averaging and programmed ventricular stimulation. Complex ventricular ectopic activity (Lown grade ≥3) was detected in 59 patients (66%). Eleven patients (12%) had episodes of nonsustained ventricular tachycardia. There were no sustained arrhythmias either on ambulatory ECG monitoring or induced by programmed ventricular stimulation. Only 1 patient had ventricular late potentials recorded by the signal-averaged electrocardiogram. There was therefore little to suggest an underlying arrhythmogenic substrate in these patients.

Continued on page A35

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- Smooth, controlled 24-hour delivery of quinidine sulfate
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- No difference in GI tolerability compared with quinidine gluconate[2]
- The most frequently prescribed quinidine brand[3]

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See brief summary of prescribing information on adjacent page.

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QuinidexExtentabs®

(quinidine sulfate extended-release tablets, USP) 300 mg

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The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General* – All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients – As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests – Periodic blood counts and liver and kidney function tests should be performed during long term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery – There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers – Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use – There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal – Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular – Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System – Headache, vertigo, apprehension, excitement, confusion delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic – Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic – Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity – Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic – Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic – Systemic lupus erythematosus, lupus nephritis.

Miscellaneous – Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

References

1. Wright GJ. Relative bioavailability and dosage form performance from single doses of quinidine as Quinidex Extentabs®, Quinaglute® Dura-Tabs®, and Quinora® in healthy male volunteers. Data on file, A.H. Robins Co., 1981.
2. Morganroth J, Hunter H. Comparative efficacy and safety of short-acting and sustained-release quinidine in the treatment of patients with ventricular arrhythmias. *Am Heart J.* 1985;110:1176-1181.
3. IMS National Prescription Audit, May 1990.

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918

Comparative Effects of Fenoldopam Mesylate and Nitroprusside on Left Ventricular Performance in Severe Systemic Hypertension

Béla B. Hackman, Beate Griffin, Mary Mills, and Kodangudi B. Ramanathan

The effects of fenoldopam (n = 15), a selective dopamine-1 agonist, and nitroprusside on left ventricular function were assessed in 19 severely hypertensive subjects (diastolic blood pressure >120 mm Hg) using radionuclide ventriculography. Fenoldopam produced greater increments in ejection fraction (+22 vs +8%; p = 0.04) and end-systolic pressure/volume ratio (+43 vs +6%; p = 0.007), and a greater reduction in relative end-systolic volume (−35 vs −20%; p = 0.04) than did nitroprusside, despite smaller reductions in blood pressure (−12 vs −22%; p = 0.002). These findings suggest an effect of fenoldopam on ventricular performance, which is independent of afterload reduction.

923

Comparison of Angiotensin-Converting Enzyme Inhibitors and Calcium Antagonists in the Treatment of Mild to Moderate Systemic Hypertension, According to Baseline Ambulatory Blood Pressure Level

Daniel Herpin, Bernard Vaisse, Muriel Pitiot, Régis de Gaudemaris, Jean-Michel Mallion, Louis Poggi, and Jean Demange

The ambulatory blood pressure (BP) recordings of 236 patients who were given either an angiotensin-converting enzyme inhibitor (n = 115) or a calcium antagonist (n = 121) were retrospectively reviewed. Patients were classified according to the difference between their observed and predicted ambulatory BP (the latter being calculated by regressing the former on the clinic BP). In patients with higher than predicted ambulatory BP level, angiotensin-converting enzyme inhibitors and calcium antagonists resulted in a roughly similar effect; conversely, in patients with lower than predicted ambulatory BP, angiotensin-converting enzyme inhibitors reduced both ambulatory systolic and diastolic BP to a greater extent than calcium antagonists did (p <0.0001, p = 0.04). Further analysis showed ambulatory BP not to be significantly decreased with calcium antagonists and angiotensin-converting enzyme inhibitors in patients whose baseline levels were <135/85 and <120/80 mm Hg, respectively.

VALVULAR HEART DISEASE

927

Effect of Aortic Valve Stenosis (Pressure Overload) and Regurgitation (Volume Overload) on Left Ventricular Systolic and Diastolic Function

Bruno Villari, Otto M. Hess, Philipp Kaufmann, Otto N. Krogmann, Joerg Grimm, and Hans P. Krayenbuehl

This study evaluates the interrelation between measures of systolic and diastolic function in chronic pressure and volume overload, and defines the

role of diastolic function parameters in the assessment of left ventricular functional derangement in the presence of normal systolic contractile function. Among the measures reflecting diastolic ventricular function (relaxation, filling and passive diastolic properties), only the time constant of pressure decay, and the constant of myocardial stiffness are correlated to systolic ejection fraction. Alterations of relaxation and passive elastic myocardial properties precede depression of systolic contractile function in 50% of patients with aortic stenosis and in 91% with aortic regurgitation. A reduction in peak filling rate (either early or late) occurs infrequently in patients with aortic valve disease.

CARDIOMYOPATHY

935
Clinical Course of Middle-Aged Asymptomatic Patients with Hypertrophic Cardiomyopathy

Gabriela M. Hecht, Julio A. Panza, and Barry J. Maron

Patients with hypertrophic cardiomyopathy (HC) may present a wide spectrum of clinical and morphologic manifestations. To further understanding of the natural history of HC, 31 middle-aged patients (aged 35 to 55 years) who initially presented with no or minimal symptoms were analyzed; 29 of these were followed for ≥2 years (range to 11.5, mean 8). Of the 29 patients, 22 are presently free of important cardiac symptoms, but 3 showed progression of symptoms, and 4 died suddenly. Annual mortality rate was 1.7%. In conclusion, of those patients with HC who achieved middle-age without developing important symptoms, 22 (76%) remained asymptomatic over the ensuing average 8-year period of evaluation. However, such patients are not protected from unfavorable clinical events, as evidenced by the fact that 7 (24%) had symptomatic deterioration or sudden cardiac death during follow-up.

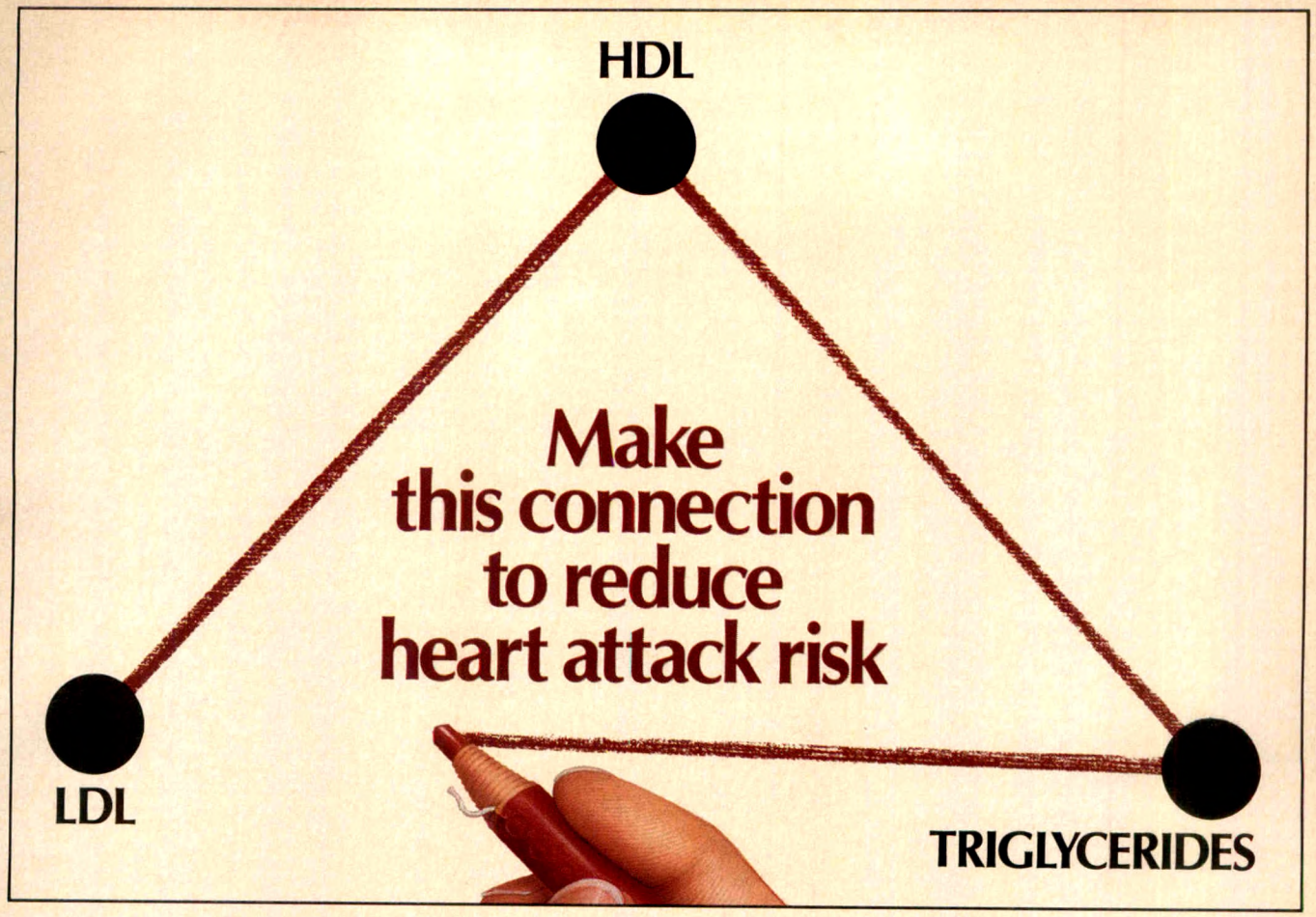
CONGENITAL HEART DISEASE

941
Comparison of Magnetic Resonance Imaging with Cross-Sectional Echocardiography in the Assessment of Left Ventricular Myocardial Mass in Children Without Heart Disease and in Aortic Isthmic Coarctation

Michael Vogel, Heiko Stern, Richard Bauer, and Konrad Bühlmeyer

To validate cross-sectional echocardiographic left ventricular (LV) mass determination, data from LV mass assessed by magnetic resonance imaging (MRI) were compared in 14 children aged 5.3 years (10 days to 14.7 years) with a mean body surface area of 0.78 m^2 (range 0.25 to 1.61). MRI was considered to be a good reference method, because there is usually no problem in defining endo- and epicardial borders. With cross-sectional echocardiography the mass was 55 g (range 12 to 126) or 64 g/m^2 (range 46 to 79), and with MRI it was 60 g (range 33 to 87) or 69 g/m^2 (range 46 to 89). The regression analysis yielded an r value of 0.98 with a standard error of the estimate of 5.7 g or a 10% difference. It is

Continued on page A43



LOPID® (gemfibrozil)



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Reduced the incidence of heart attack* 71%

—in a high-risk subgroup of Helsinki Heart Study (HHS) patients with a triad of lipid disorders: coexisting low HDL, high triglycerides, and high LDL. While the overall reduction in heart attack in the HHS was 34%, the greatest reduction was achieved among these LOPID patients with baseline triglycerides >200 mg/dL and baseline LDL/HDL ratio >5 (n = 154).†[1]

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LOPID is indicated for reducing the risk of coronary heart disease in type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.

Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.

†Mean HDL = 35 mg/dL; mean LDL = 208 mg/dL; $P = .005$; 95% CI 21.2 to 118.6.

Reference 1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation.* 1992;85:37-45.

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PARKE-DAVIS

BOOTS PHARMACEUTICALS

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, postcholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

Caution – Federal law prohibits dispensing without prescription.

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PD-55-JA-7731-A1(032)

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RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
DRAMATICALLY REDUCES HEART ATTACK


There is a safer way
to get a great picture.
Nonionic
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(ioversol)

And a safer way to great cardiac imaging.

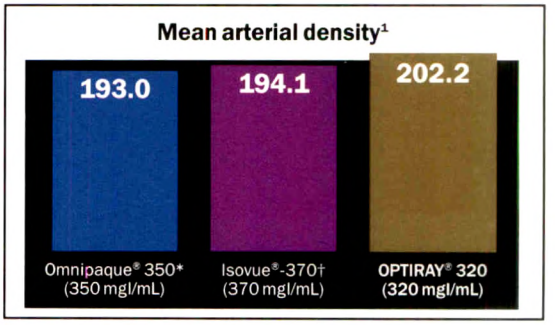


Also available in a 35% concentration: OPTIRAY® 350 (ioversol injection 74%)

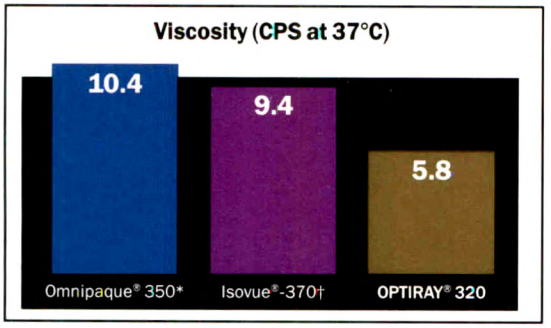
Great cardiac visualization with the safety of lower iodine...

A recent clinical study showed that OPTIRAY® 320 (ioversol injection 68%) provides equivalent image density when compared with contrast agents of higher iodine concentration.[1]

So OPTIRAY® 320 provides a means for reducing the amount of iodine administered with no reduction in overall image quality. And a lower iodine dose may reduce the likelihood of renal dysfunction.[2]

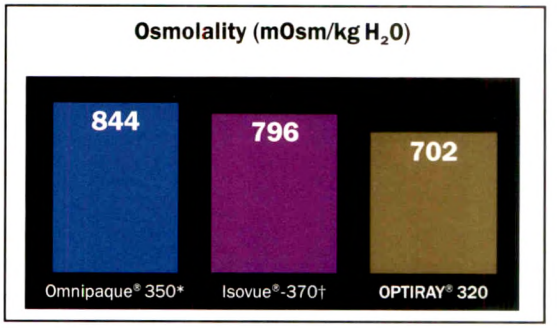


lower viscosity...



The low viscosity and greater flow rate of OPTIRAY® 320 mean easier hand injections and images equivalent to contrast agents with a higher iodine concentration.[1]

and lower osmolality.



OPTIRAY® 320 has the lowest osmolality of these nonionic contrast media.

Sometimes all you need is a little less, to get more.

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

References:
1. Kern MJ, Roth RA, Aguirre FV, Beauman G, Vogel R. Effect of viscosity and iodine concentration of nonionic radiographic contrast media on coronary arteriography in patients. *Am Heart J.* 1992; 123:160-165. 2. Gomes AS, Baker JD, Martin-Paredero V, et al. Acute renal dysfunction after major arteriography. *AJR.* 1985; 145:1249-1253.

*Omnipaque® (iohexol) — Winthrop Pharmaceuticals
†Isovue® (iopamidol) — E.R. Squibb & Sons, Inc.

Please see the following page for a brief summary of prescribing information.

Nonionic
OPTIRAY®
(ioversol)

A safer way to great imaging

OPTIRAY® 160 240 320 350
(Ioversol Injection)

DESCRIPTION: Each milliliter of OPTIRAY 160 (ioversol injection 34%) provides 339 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 160 provides 16% (160 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 240 (ioversol injection 51%) provides 509 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 240 provides 24% (240 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 320 (ioversol injection 68%) provides 678 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 320 provides 32% (320 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 350 (ioversol injection 74%) provides 741 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 350 provides 35% (350 mg/mL) organically bound iodine.

CONTRAINDICATIONS: None.

WARNINGS: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious or fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. A cause-effect relationship to the contrast medium has not been established since the patients' pre-existing condition and procedural technique are causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered.

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication to the procedure; however, special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when administered intravascularly.

Reports of thyroid storm following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients before use of any contrast medium.

PRECAUTIONS: *General:* Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible non-diabetic patients (often elderly with pre-existing renal disease). *Patients should be well hydrated prior to and following the administration of OPTIRAY.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See ADVERSE REACTIONS). Increased risk is associated with a history of previous reaction to a contrast medium, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of exposure to the contrast agent.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to insure proper catheter placement are suggested.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thromboses and embolism.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic disturbances which may be associated with a transitory increase in the circulating osmotic load.

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

Extreme caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Drug Interactions: Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received a cholecystographic contrast agent.

Other drugs should not be mixed with ioversol injection.

Drug Laboratory Test Interactions: The results of PBI and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility.

Pregnancy Category B: No teratogenic effects attributable to ioversol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether ioversol crosses the placental barrier or reaches fetal tissues. However, many injectable contrast agents cross the placental barrier in humans and appear to enter fetal tissue passively. Because animal teratology studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. X-ray procedures involve a certain risk related to the exposure of the fetus.

Nursing Mothers: It is not known whether ioversol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Adverse reactions following the use of OPTIRAY formulations are usually mild to moderate, of short duration and resolve spontaneously (without treatment). However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media.

Injections of contrast media are often associated with sensations of warmth and pain. In controlled double-blind clinical studies, significantly less warmth and pain were associated with the injection of OPTIRAY than with iothalamate meglumine, diatrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

When OPTIRAY was used for coronary arteriography and ventriculography in double-blind clinical trials, electrocardiographic and hemodynamic changes occurred with less frequency and severity with ioversol injection than with diatrizoate meglumine and diatrizoate sodium.

Following coronary artery and left ventricular injection, electrocardiographic parameters were affected less with OPTIRAY (ioversol injection) than with diatrizoate meglumine and diatrizoate sodium injection. These parameters included the following: bradycardia, tachycardia, T-wave amplitude, ST depression and ST elevation.

OPTIRAY has also been shown to cause fewer changes in cardiac function and systemic blood pressure than conventional ionic media. These include cardiac output, left ventricular systolic and end-diastolic pressure, right ventricular systolic and pulmonary artery systolic pressures and decreases in systolic and diastolic blood pressures.

The following table of incidence of reactions is based upon clinical trials with OPTIRAY formulations in over 1466 patients. This listing includes all adverse reactions which were coincidental to the administration of ioversol regardless of their direct attributability to the drug or the procedure. Adverse reactions are listed by organ system and in decreasing order of occurrence. Significantly more severe reactions are listed before others in a system regardless of frequency.

Adverse Reactions

System	> 1%	≤ 1%
Cardiovascular	none	angina pectoris hypotension blood pressure fluctuation arterial spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive	none	nausea vomiting
Nervous	none	cerebral infarct headache blurred vision vertigo lightheadedness vasovagal reaction discrimination paresthesia dysphasia muscle spasm syncope visual hallucination
Respiratory	none	laryngeal edema pulmonary edema sneezing nasal congestion coughing shortness of breath hypoxia
Skin	none	periorbital edema urticaria facial edema flush pruritus
Miscellaneous	none	extravasation hematoma shaking chills bad taste general pain

Regardless of the contrast medium employed, the overall incidence of serious adverse reaction is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography.

General Adverse Reactions to Contrast Media

The following adverse reactions are possible with any parenterally administered iodinated contrast medium. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. Based upon clinical literature, reported deaths from the administration of conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

In addition to the adverse reactions reported for ioversol, the following additional adverse reactions have been reported with the use of other contrast agents and are possible with any water soluble, iodinated contrast agent.

Nervous: convulsions, aphasia, paralysis, visual field losses which are usually transient but may be permanent, coma and death.

Cardiovascular: angioneurotic edema, peripheral edema, vasodilation, thrombosis and rarely thrombophlebitis, disseminated intravascular coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymosis and tissue necrosis.

Respiratory: choking, dyspnea, wheezing which may be an initial manifestation of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm, apnea and cyanosis. Rarely these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances and death.

Miscellaneous: hyperthermia, temporary anuria or other nephropathy.

Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

In cerebral arteriography, cardiovascular reactions that may occur with some frequency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur are: seizures, drowsiness, transient paresis, and mild disturbances in vision.

Central nervous system reactions with OPTIRAY in controlled clinical studies in cerebral arteriography that were considered drug-related and occurred with frequencies greater than 1% were: headache, bradycardia, blood pressure fluctuation, disorientation, nausea and vertigo.

In aortography, depending on the technique employed, the risks of this procedure also include the following: injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, retroperitoneal hemorrhage from the translumbar approach and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume, and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows.

There were no cardiovascular system reactions with OPTIRAY in controlled clinical studies in coronary arteriography with left ventriculography that were considered drug-related and occurred with a frequency greater than 1%.

PRECAUTIONS FOR SPECIFIC PROCEDURES:

Cerebral Arteriography

Extreme caution is advised in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Peripheral Arteriography

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all.

Coronary Arteriography and Left Ventriculography

Mandatory prerequisites to the procedure are specialized personnel, ECG monitoring apparatus and adequate facilities for immediate resuscitation and cardioversion. Electrocardiograms and vital signs should be routinely monitored throughout the procedure.

Venography

Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. In order to minimize extravasation during injection, fluoroscopy is recommended.

Intravenous Digital Subtraction Angiography

In addition to the general precautions previously described, the risks associated with IV DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

OVERDOSAGE: The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

Ioversol does not bind to plasma or serum protein and is therefore, dialyzable.

The intravenous LD_{50} values (gI/kg) for ioversol in animals were: 17 (mice), and 15 (rats).

DOSAGE AND ADMINISTRATION: Details on dosage are provided in the package insert. CONSULT FULL PACKAGE INSERT BEFORE USE.

MALLINCKRODT *Cardiology*

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concluded that cross-sectional echocardiography can reliably assess LV myocardial mass in pediatric patients.

945

Short- and Midterm Results of Balloon Valvuloplasty for Valvular Aortic Stenosis in Children

Maarten Witsenburg, Adri H. Cromme-Dijkhuis, Ingrid M. E. Frohn-Mulder, and John Hess

Twenty-one children with valvular aortic stenosis (10 of whom had undergone earlier surgical valvulotomy) underwent balloon valvuloplasty, because of a substantial gradient, ST-T changes or syncope. Valvuloplasty reduced the Doppler gradient by 48%, which persisted after 2 to 4.2 years of follow-up. ST-T changes disappeared, and syncope did not reoccur. Except for age, weight and left ventricular end-diastolic pressure before valvuloplasty, there were no differences between the earlier operated and nonoperated patients. Aortic valvuloplasty postponed surgical treatment, but induced occurrence or increase of valve regurgitation in many patients. Three patients underwent valve replacement because of aortic valve regurgitation within 2 years (all 3 had undergone earlier surgical valvulotomy).

MISCELLANEOUS

951

Circadian Variation in Platelet Function in Healthy Volunteers

Syed M. Jafri, Mike VanRollins, Tsunenori Ozawa, Eberhard F. Mammen, A. David Goldberg, and Sidney Goldstein

Circadian variation in hemostasis-related factors was evaluated in 9 healthy patients. Circadian changes occurred in β-thromboglobulin ($p < 0.05$) and platelet factor 4 ($p < 0.06$). Platelet activation was lowest with patients resting and supine, and increased with activity, with peak levels achieved at 3 P.M. ($p < 0.01$). Activation of coagulation, as determined by thrombin–antithrombin III complexes ($p = 0.44$) or D-Dimers ($p = 0.36$), did not show diurnal variation. Circadian changes in platelet function were related to activity and not to morning hours as reported by other studies.

METHODS

955

Outcome and Complications of Prolonged Intraaortic Balloon Counterpulsation in Cardiac Patients

Jason M. Lazar, Galal M. Ziady, Stephen J. Dummer, Mark Thompson, and Robert J. Ruffner

The prolonged use of the intraaortic balloon pump in patients with end-stage heart disease was studied in 49 patients retrospectively. All patients needed the support for ≥ 5 days. Insertion of the balloon catheter was performed percutaneously, and the duration of insertion ranged from 5 to

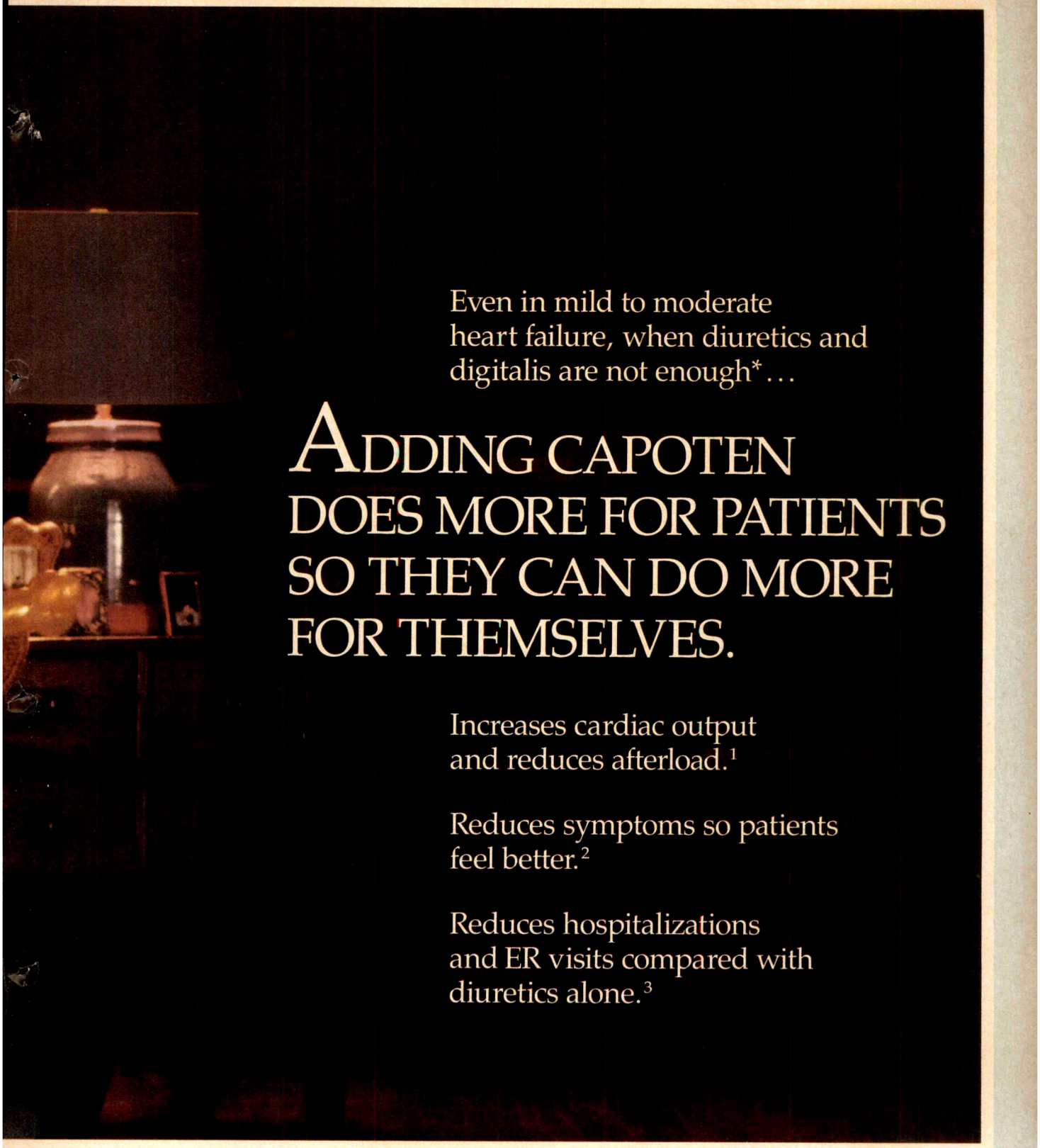
Continued on page A47



CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

***CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.**

Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the last page of this ad.



Even in mild to moderate heart failure, when diuretics and digitalis are not enough*...

ADDING CAPOTEN DOES MORE FOR PATIENTS SO THEY CAN DO MORE FOR THEMSELVES.

Increases cardiac output and reduces afterload.[1]

Reduces symptoms so patients feel better.[2]

Reduces hospitalizations and ER visits compared with diuretics alone.[3]

IN HEART FAILURE

CAPOTEN®
(captopril)

12.5 mg, 25 mg, 50 mg, 100 mg Scored Tablets

CAPOTEN® TABLETS
Captopril Tablets

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS: Angioedema–Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia/Agranulocytosis–Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS [Drug Interactions].) In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors, including CAPOTEN, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

Captopril crosses the human placenta. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the fetus; limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation have been reported in association with oligohydramnios. Patients who do require ACE inhibitors during the second and third trimester of pregnancy should be apprised of the potential hazards to the fetus, and frequent ultrasound examinations should be performed to look for oligohydramnios. If oligohydramnios is observed, CAPOTEN should be discontinued unless it is considered life-saving to the mother.

Other potential risks to the fetus/neonate exposed to ACE inhibitors include: prematurity, patent ductus arteriosus; fetal death has also been reported. It is not clear, however, whether these reported events are related to ACE inhibition or the underlying maternal disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

Captopril was embryocidal in rabbits when given in doses about 2 to 70 times (on a mg/kg basis) the maximum recommended human dose, and low incidences of craniofacial malformations were seen. These effects in rabbits were most probably due to the particularly marked decrease in blood pressure caused by the drug in this species.

Captopril given to pregnant rats at 400 times the recommended human dose continuously during gestation and lactation caused a reduction in neonatal survival.

No teratogenic effects (malformations) have been observed after large doses of captopril in hamsters and rats.

If CAPOTEN is used during pregnancy or if the patient becomes pregnant while taking CAPOTEN, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General: *Impaired Renal Function*–Hypertension–Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure–About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Hyperkalemia:* Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.) *Valvular Stenosis*–A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*–If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension–Patients on Diuretic Therapy*–Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity–In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release–Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity–The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium–Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis–Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Lithium–Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category D: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use: Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less that that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, (usually maculopapular, rarely urticarial) often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension with captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials.

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality: In infants exposed *in utero* to ACE inhibitors the following adverse experiences have been reported: fetal and neonatal death, renal failure, hypoplastic lung development, hypotension, hyperkalemia, skull hypoplasia, limb contractures, craniofacial deformities, intrauterine growth retardation, prematurity and patent ductus arteriosus (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Altered Laboratory Findings: *Serum Electrolytes: Hyperkalemia:* small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of: 12.5 mg in bottles of 100 and 1000; 25 mg in bottles of 100 and 1000; 50 mg in bottles of 100 and 1000; 100 mg in bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets.

(J3-658W)

References: 1. Physicians' Desk Reference®, 45th ed, Oradell, NJ, Medical Economics Co Inc, 1991, pp 2141-2143. 2. Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *JACC* 2:755-763, 1983. 3. The Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539-544, 1988.

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46 days. Mean systemic arterial pressure did not change with balloon insertion. Both mean pulmonary artery and pulmonary arterial wedge pressures decreased (33 ± 8 to 26 ± 9 mm Hg [p <0.01], and 25 ± 8 to 17 ± 6 mm Hg [p <0.01], respectively). Cardiac index increased from 1.6 ± 0.4 to 2.2 ± 0.5 liters/min/m^2 on insertion and continued to increase to 2.7 ± 0.5 liters/min/m^2 (p <0.01) before removal. Complications were observed, including infection of the balloon catheter in 7 patients, and hemorrhage in an additional 7. Eleven patients had vascular compromise. Progressive heart and multiple organ failure was the cause of death in 20 patients, and 19 survived to receive the left ventricular assist device and heart transplantation. Only 10 patients were weaned off the balloon.

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TENORMIN® (atenolol) 25, 50, 100 mg tablets

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patient should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta, selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta, selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta,-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents; eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyreidism. Patients suspected of having thyroid disease should be monitored closely when administering TENORMIN I.V. Injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (SEE DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Caution should be exercised with TENORMIN I.V. Injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibrcadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test *(S typhimurium).*

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommenced human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

Usage in Pregnancy: Pregnancy Category C: Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.* There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

	Volunteered (US Studies)		Total - Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

	Conventional Therapy Plus Atenolol (n=244)		Conventional Therapy Alone (n=233)	
Bradycardia	43	(18%)	24	(10%)
Hypotension	60	(25%)	34	(15%)
Bronchospasm	3	(1.2%)	2	(0.9%)
Heart Failure	46	(19%)	56	(24%)
Heart Block	11	(4.5%)	10	(4.3%)
BBB + Major Axis Deviation	16	(6.6%)	28	(12%)
Supraventricular Tachycardia	28	(11.5%)	45	(19%)
Atrial Fibrillation	12	(5%)	29	(11%)
Atrial Flutter	4	(1.6%)	7	(3%)
Ventricular Tachycardia	39	(16%)	52	(22%)
Cardiac Reinfarction	0	(0%)	6	(2.6%)
Total Cardiac Arrests	4	(1.6%)	16	(6.9%)
Nonfatal Cardiac Arrests	4	(1.6%)	12	(5.1%)
Deaths	7	(2.9%)	16	(6.9%)
Cardiogenic Shock	1	(0.4%)	4	(1.7%)
Development of Ventricular Septal Defect	0	(0%)	2	(0.9%)
Development of Mitral Regurgitation	0	(0%)	2	(0.9%)
Renal Failure	1	(0.4%)	0	(0%)
Pulmonary Emboli	3	(1.2%)	0	(0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

	Reasons for Reduced Dosage IV Atenolol Reduced Dose (< 5mg)*		Oral Partial Dose	
Hypotension/Bradycardia	105	(1.3%)	1168	(14.5%)
Cardiogenic Shock	4	(.04%)	35	(.44%)
Reinfarction	0	(0%)	5	(.06%)
Cardiac Arrest	5	(.06%)	28	(.34%)
Heart Block (> first degree)	5	(.06%)	143	(1.7%)
Cardiac Failure	1	(.01%)	233	(2.9%)
Arrhythmias	3	(.04%)	22	(.27%)
Bronchospasm	1	(.01%)	50	(.62%)

*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with TENORMIN, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, impotence, Peyronie's disease, psoriasiform rash; reversible alopecia, and thrombocytopenia. TENORMIN, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis, purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash, Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (SEE DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: Overdosage with TENORMIN has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following TENORMIN overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in TENORMIN overdose are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENORMIN can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta, stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. Injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued.

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Elderly Patients or Patients with Renal Impairment: TENORMIN is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m². Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

The following maximum oral dosages are recommended for elderly, renally-impaired patients and for patients with renal impairment due to other causes:

Creatinine Clearance (mL/min/1.73m²)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50mg daily
<15	>27	25mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of TENORMIN: 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: TENORMIN Tablets: Tablets of 25 mg atenolol, NDC 0310-0107 (round, flat, uncoated white tablets with "T" debossed on one side and 107 debossed on the other side) are supplied in bottles of 100 tablets.

Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in well-closed, light resistant containers.

TENORMIN I.V. Injection: TENORMIN I.V. Injection, NDC 0310-0108, is supplied as 5 mg atenolol in 10 mL ampules of isotonic citrate-buffered aqueous solution.

Protect from light. Keep ampules in outer packaging until time of use. Store at room temperature.

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Improved Stenosis Geometry by Quantitative Coronary Arteriography After Vigorous Risk Factor Modification

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This study is a randomized, controlled, blinded, arteriographic trial to determine the effects of a low-cholesterol, low-fat, vegetarian diet, stress management and moderate aerobic exercise on geometric dimensions, shape and fluid dynamic characteristics of coronary artery stenoses in humans. Complex changes of different primary stenosis dimensions in opposite directions or to different degrees cause stenosis shape change with profound effects on fluid dynamic severity, not accounted for by simple percent narrowing. Accordingly, all stenosis dimensions were analyzed, including proximal, minimal, distal diameter, integrated length, exit angles and exit effects, determining stenosis shape and a single integrated measure of stenosis severity, stenosis flow reserve reflecting functional severity. In the control group, complex shape change and a stenosis — molding characteristic of statistically significant progressing severity occurred with worsening of stenosis flow reserve. In the treated group, complex shape change and stenosis molding characteristic of significant regressing severity was observed with improved stenosis flow reserve, thereby documenting the multidimensional characteristics of regressing coronary artery disease in humans.

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The Lifestyle Heart Trial[1] is a randomized, controlled, blinded, arteriographic trial to test the hypothesis that (1) vigorous modification of risk factors stops progression or causes regression of coronary artery stenosis, and (2) stenosis shape changes or undergoes remolding with progression or regression of coronary atherosclerosis in humans to the extent that no single dimension reflects the essential changes observed.

The initial report of this trial[1] describes the experimental design, risk factor intervention and changes in percent diameter stenosis because percent diameter stenosis is the most widely used measure of stenosis severity. However, percent stenosis is an incomplete measure of stenosis severity because length, absolute lumen area and shape effects are not accounted for and correlate poorly with the functional measure of coronary artery stenoses, coronary flow reserve.[2–10] The cumulative effects of multidimensional geometric changes on fluid dynamic characteristics of stenoses suggest that simple concepts of progression/regression need to be redefined in terms of shape changes or remolding of stenoses. Therefore, to definitively address whether progression or regression occurs in humans with risk factor modification, we performed multidimensional analysis of arteriographic stenoses to determine stenosis flow reserve as a single functional measure of severity incorporating all geometric dimensions of each stenosis.

Background: Seven previous coronary arteriographic trials of cholesterol lowering by diet and drugs have been reported.[11–17] Kuo et al[11] and the Leiden Intervention Trial[12] suggested that progression of stenoses was prevented by a cholesterol-lowering diet and drugs but these studies lacked untreated control subjects. Nash[13] and Nikkila[14] and their co-workers showed prevention of progression by cholesterol-lowering drugs compared with untreated control subjects who were not randomized. In a randomized controlled trial of clofibrate, Cohn et al[15] showed equal progression of disease in 63 and 69% of treated and control groups without regression.

The National Heart, Lung, and Blood Institute Type II Coronary Intervention Study[16] was a randomized, controlled trial of diet and cholestyramine showing less arteriographic progression (32%) in the treated

group compared with a progression of 49% in the control group, a significant difference. However, no regression was observed, and 32% of the treated group still showed progression of disease. The Cholesterol Lowering Atherosclerosis Study trial[17] was a randomized controlled arteriographic trial of diet, colestipol and niacin showing regression in 16% of treated patients compared with 2% regression in control groups. Appearance of new lesions was prevented and global severity scores were significantly less in the treated group compared with control subjects. However, in the treated group 39% still showed progression of disease. Ornish et al[1] demonstrated cessation of progression or regression of coronary artery stenoses in a large proportion of subjects on a strict low-fat vegetarian diet but not in control subjects on a standard American Heart Association diet.[1] Brown et al[18] demonstrated significant regression in subjects with familial hypercholesterolemia treated by double drug therapy for reducing serum cholesterol.

METHODS

Automated quantitative arteriographic analysis was used in this study because (1) complex shape changes of stenosis are accounted for with incorporation of all dimensions of length, percent narrowing, absolute lumen area and shape effects; (2) visual interpretations of arteriograms are marked by such great interobserver and intraobserver variation that comparisons of arteriograms from different subjects or the same subject at different times have limited quantitative accuracy for assessing severity or changes in severity of stenoses[2-10]; (3) the reproducibility of automated quantitative coronary arteriographic analysis of primary dimensions in vivo is ± 3 to ± 5% in absolute dimensions, with a precision in phantoms of ± 0.1 mm[2,4-7,19-21] so that small changes in stenosis geometry could be reliably measured in control and treated groups; and (4) no previous study has used automated quantitative coronary arteriography or measured all stenosis dimensions in order to define the total geometric changes occurring with regression or progression.

Study patients: Patients were men or women, 35 to 70 years old, who had documented coronary artery disease by arteriography, had no recent myocardial infarction or were not taking lipid-lowering drugs, had left ventricular ejection fraction >25%, and resided in the San Francisco area to participate in the risk modification program. After all groups gave informed consent and were randomized initial and follow-up, coronary arteriography was performed using the standard percutaneous femoral approach as previously described.[1,2]

Modification of risk factors was achieved by the Preventive Medicine Research Institute in San Francisco as previously described[1] and summarized here. It consisted of a low-cholesterol (<5 mg/day), low-fat (<10% of calories) vegetarian diet with 15% protein and 75% complex carbohydrate augmented with vitamin B-12. Patients stopped smoking, practiced stress management, and participated in moderate aerobic exercise on a daily basis.

Quantitative coronary arteriography: The cardiac catheterization laboratories in San Francisco were calibrated for quantitative arteriographic analysis by the University of Texas staff. Meticulous records of the view angles, x-ray exposures, image intensifier, x-ray tube, patient distances and reference catheter dimensions were maintained. Follow-up arteriograms used these same characteristics in order to reproduce views and exposures as closely as possible on follow-up studies.

Initial and follow-up arteriograms were analyzed simultaneously in pairs by a technician unaware of clinical data or group assignment using automated border recognition and stenosis analysis techniques in order to avoid the potential bias, imprecision and uncertainties of visual interpretation. Cine arteriographic frames of orthogonal views were digitized on a Spatial Data System, Eyecom II online with a VAX 11/780 for each stenosis involving a major artery. Absolute and relative stenosis dimensions were measured with a computer program providing automatic detection of vessel borders (Figure 1). The theory and equations for predicting stenosis flow reserve from these dimensions have previously been described.[2,5-7,19-21]

The primary stenosis dimensions measured by the automated arteriographic program include proximal diameter and cross-sectional lumen area, minimal diameter and area, distal diameter and area, the exit angle, exit shape effects, and calculated measures of severity including percent diameter stenosis, percent area narrowing, integrated length-area effects and stenosis flow reserve.

Stenosis flow reserve is a measure of severity integrating all these dimensions into a single number reflecting the capacity for increasing flow through the observed geometry for a standardized aortic pressure. It is based on the concept of coronary flow reserve proposed 17 years ago by Gould et al[2,3] that has evolved into an accepted measure of functional stenosis severity.[2-10,19-21] Our arteriographic analysis has been validated in 3 separate experimental studies,[4,7,21] applied in humans[2,19] and used routinely in approximately 4,000 clinical arteriograms.

Figure 1 illustrates the pressure flow relation for a stenosis based on all its arteriographic dimensions, shown by the downward curving. Stenosis flow reserve is defined as the intersection of the downward curved line characterizing stenosis severity by stenosis geometry with the experimentally determined upward straight line characterizing maximal flow for given pressure in a maximally vasodilated coronary artery bed.[2,7] Flow is expressed as a relative multiple of rest flow, Q/Qrest under standardized hemodynamic conditions of 100 mm Hg aortic pressure, and standardized normal maximal flow reserve of 5 times baseline. Compared with direct measurements by electromagnetic flow meter in experimental animals, there is a close correlation between arteriographic stenosis flow reserve based on arteriographic dimensions and directly measured coronary flow reserve by flow meter for comparable hemodynam-

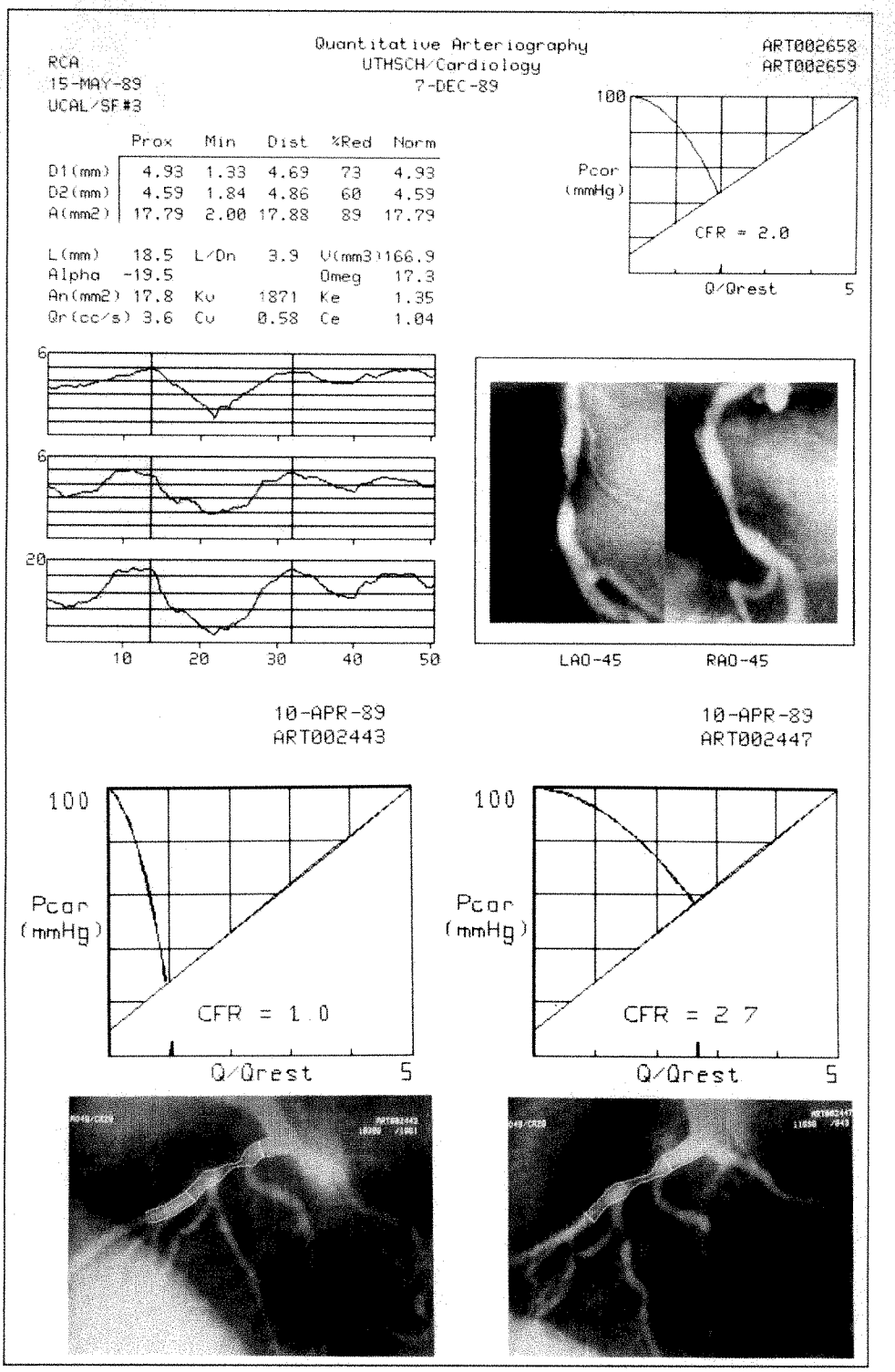


FIGURE 1. ***Top,*** **quantitative arteriographic data for each patient showing stenosis dimensions including minimal (Min), proximal (Prox) and distal (Dist) absolute lumen diameters, percent diameter stenosis in each view (D_1, D_2), minimal, proximal and distal cross-sectional lumen area and percent area stenosis, volume, length, area-length of the stenosed segment, entrance and exit angles, and fluid dynamic coefficients characterizing viscous and expansion losses (Cv, Ce, Kv and Ke)** ***(upper left). Lower left graphs*** **show diameters in 2 views and cross-sectional lumen area as functions of axial position. The** ***graph*** **on the** ***upper right*** **shows determination of stenosis coronary flow reserve (CFR). The** ***upward slanting, straight diagonal line*** **representing maximal arteriolar vasodilation in the absence of a stenosis crosses the downward curving pressure-flow relation characteristic of the stenosis. Stenosis flow reserve in this example is 2.0, determined as the maximal flow relative to resting flow (Q/Qrest) for a given stenosis geometry under standardized hemodynamic conditions of 100 mm Hg aortic pressure and normal stenosis flow reserve of 5.** ***Bottom,*** **2 sequential studies showing regression with improvement in stenosis flow reserve from 1.0 to 2.7. LAO = left anterior oblique; Norm = normal; RAO = right anterior oblique.**

ic conditions.[2,7,21] The 95% confidence interval for stenosis flow reserve was ± 0.66, with a reproducibility of primary dimensions of ± 3 to ± 5%.[2,4–7,19–21] The advantages of measuring stenosis flow reserve compared with single stenosis dimensions such as percent stenosis mentioned before have been discussed in detail elsewhere.[2–10,19–21]

Our quantitative arteriographic method is similar to that of Brown et al,[22,23] but was developed independently and in parallel using automated border recognition rather than visual tracing to determine stenosis dimensions.[2,5–7,19–21] It also differs by taking into account length-dependent exit effects not previously accounted for, and determines stenosis flow reserve as a single integrated measure of stenosis severity taking into account all stenosis dimensions.

Because different stenosis dimensions often change in opposite directions, the definitions of progression, regression and molding of stenoses are necessary. Figure 2 illustrates what we have termed simple regression in which all primary dimensions of proximal, minimal and distal diameters improve, the exit angle becomes smaller or more streamlined, percent diameter narrowing decreases and stenosis flow reserve increases. In simple progression all of these measurements become worse.

Figure 3 shows more complex changes in which (top panel) proximal and distal diameters worsen (progression), the narrowest segment remains unchanged (stabilization or no progression), while percent diameter lessens and stenosis flow reserve increases reflecting overall improvement or diminution in severity (regression). The middle panel of Figure 3 shows worsening of distal and proximal diameters, enlargement or regression of the narrowest segment, lessening of percent diameter stenosis with more improvement in stenosis flow reserve. We term this pattern remolding or a shape change of the stenosis that leaves a diffusely narrower artery than normal but with less segmental narrowing and improved flow capacity. Because overall flow capacity or stenosis flow reserve is improved, this pattern of remolding is characteristic of regression. The lowest panel of Figure 3 shows narrowing of proximal and distal segments to a greater extent than the narrowest segment, thereby causing improved, less severe percent diameter stenosis, but stenosis flow reserve or flow capacity is worse, a pattern that is one form of remolding with progression of disease.

Data analysis: Individual stenosis dimensions were analyzed as continuous variables from the first to the second arteriogram within the treatment, control or subgroups with standard 2-tailed, paired *t* tests comparing arteriograms at entry to follow-up arteriograms[24] and with unpaired *t* tests[24] and analysis of variance[1] for comparisons between control and treated or subgroups. Because significance and conclusions were the same by analysis of variance and by *t* testing, the latter are reported here since they are more familiar to most readers.

In the initial report of this trial using percent stenoses as the primary end point,[1] between-group comparisons included coronary lesions that progressed to total occlusion during the year since such an event is an important clinical end point. Because the current report focuses on changes in stenosis geometry, those stenoses that progressed to occlusion, or occluded arteries that opened during the trial in both control and treatment groups (a total of 6 of 198 stenoses), were excluded from analysis in this report. This exclusion was necessary because potentially large incremental changes due possibly to thrombosis or thrombolysis could bias mean values of shape change due to atheromatous alterations in other stenoses. Analysis of all data including stenoses progressing to occlusion or occluded arteries opening during the trial showed greater, more significant differences between control and treated groups but was not different from the more conservative results excluding those instances, as reported later. Of 48 patients enrolled, 7 did not have follow-up angiographic data[1] and 1 additional patient was excluded because the only end point was a total occlusion that became patent. Therefore the data base for this report is 40 patients.

RESULTS

In all, 40 patients having 192 stenoses, or 4.8 stenoses per patient, were analyzed, with 18 patients having

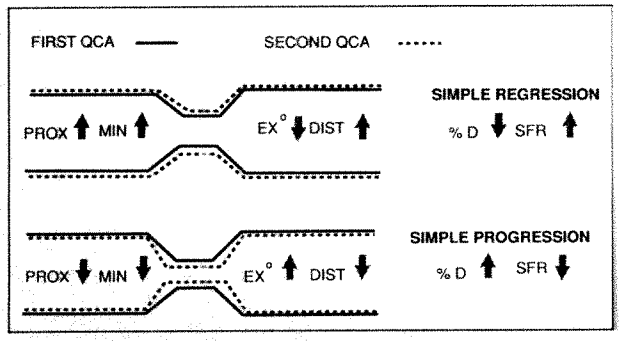


FIGURE 2. Patterns of changing coronary artery stenoses. DIST = distal diameters; % D = percent diameter stenosis; EX° = exit angle; MIN = minimum; PROX = proximal; QCA = quantitative coronary arteriography showing simple progression and regression; SFR = stenosis flow reserve accounting for all stenosis dimensions.

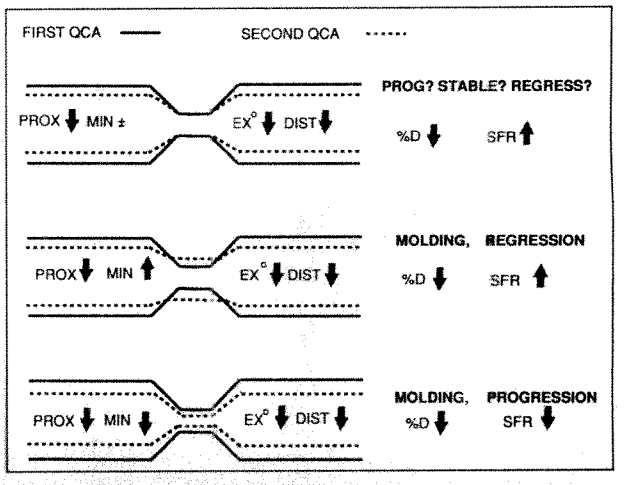


FIGURE 3. Patterns of changing coronary artery stenoses. Complex changes of stenosis dimensions in opposite directions with shape change or remolding during progression (PROG) or regression. Abbreviations as in Figure 2.

TABLE I Stenosis Dimension Changes

	PROX (mm)	MIN (mm)	EX° (deg.)	DIST (mm)	% DS	SFR
Control Subjects (87 stenoses)						
QCA1	3.07	1.75	12.7	2.84	42.7	3.90
QCA2	2.98	1.64	14.0	2.71	44.4	3.79
ΔQCA 2-1	−0.10	−0.12	+1.14	−0.14	+1.75	−0.11
p for Δ	0.01	0.001	NS	0.000	NS	NS
Treated Subjects (105 stenoses)						
QCA1	2.86	1.67	16.0	2.67	40.1	3.94
QCA2	2.78	1.67	16.1	2.55	38.0	4.07
ΔQCA 2-1	−0.08	+0.007	−0.91	−0.11	−2.1	+0.13
p for Δ	0.02	NS	NS	0.001	0.03	0.03
p for ΔT vs ΔC	NS	0.008	NS	NS	0.006	0.01

C = control; deg. = degree; % DS = percent diameter stenosis; DIST = distal diameter just distal to stenosis; EX° = exit angle; MIN = minimal diameter at narrowest point; NS = not significant; PROX = proximal diameter just proximal to stenosis; QCA = quantitative coronary arteriography; SFR = stenosis flow reserve; T = treated.

TABLE II Baseline Severity and Stenosis Dimension Changes

	PROX (mm)	MIN (mm)	EX° (deg.)	DIST (mm)	% DS	SFR
Mild, Control (74 stenoses)						
QCA1	3.15	1.91	12.2	2.94	38.2	4.26
QCA2	3.04	1.78	13.7	2.82	40.8	4.07
ΔQCA 2-1	−0.11	−0.14	+1.47	−0.12	+2.6	−0.19
p for Δ	0.015	0.001	NS	0.004	0.015	0.011
Mild, Treated (88 stenoses)						
n = 88						
QCA1	2.83	1.81	10.7	2.65	35.0	4.33
QCA2	2.76	1.78	10.2	2.55	34.3	4.32
ΔQCA 2-1	−0.06	−0.03	−0.54	−0.09	−0.7	−0.01
p for Δ	NS	NS	NS	0.006	NS	NS

Mild = baseline stenosis flow reserve ≥ 3; other abbreviations as in Table I.

TABLE III Baseline Severity and Stenosis Dimension Changes

	PROX (mm)	MIN (mm)	EX° (deg.)	DIST (mm)	% DS	SFR
Severe, Control (13 stenoses)						
QCA1	2.59	0.82	15.7	2.30	68.4	1.82
QCA2	2.60	0.89	15.7	2.12	65.1	2.17
ΔQCA 2-1	+0.00	+0.06	−0.05	−0.17	−3.3	+0.35
p for Δ	NS	NS	NS	NS	NS	NS
Severe, Treated (17 stenoses)						
QCA1	3.06	0.96	16.3	2.79	66.5	1.94
QCA2	2.87	1.14	12.7	2.55	57.2	2.79
ΔQCA 2-1	−0.19	+0.17	−3.6	−0.24	−9.3	+0.85
p for Δ	0.014	0.002	NS	0.048	0.001	0.000

Severe = baseline stenosis flow reserve < 3; other abbreviations as in Table I.

87 coronary artery stenoses in the control group and 22 patients having 105 stenoses in the treated group. The mean interval between the first and second arteriogram was 15 ± 3 months as either a control or treatment subject.

Table I lists the dimension changes in control and treated groups with the statistical significance of each change. Figure 4 illustrates these changes and the statistical significance of the difference in each dimensional change between the control and treated subjects. In both groups, both proximal and distal diameters significantly decreased. The minimal diameter decreased further or progressed in controls but did not progress in the treated group. Percent diameter stenosis and stenosis flow reserve worsened somewhat in the control subjects, although not significantly, improved significantly in the treated group, and the changes from the first to the second study between the control and treated groups were statistically significant.

Tables II and III and Figure 5 show changes in stenosis dimensions for lesions that were initially mild (stenosis flow reserve ≥3) or initially severe (stenosis flow reserve <3) at the baseline entry study. For baseline mild lesions (Table II) in the control group, proximal, minimal, distal diameters, percent diameter stenosis and stenosis flow reserve all worsened significantly, reflecting simple progression of all dimensions. Baseline mild lesions in the treatment group remained stable with no change in proximal and minimal diameters, percent diameter stenosis and stenosis flow reserve, all indicating that progression was prevented; distal diameter decreased slightly but had little effect on flow reserve.

Baseline severe lesions in the control group showed no significant change during the study (Table III). Baseline severe lesions of the treated group showed mild, statistically significant, increased narrowing of proximal and distal diameters, enlargement of the minimal diameter, a decrease of −9.3% diameter stenosis units, and improved stenosis flow reserve, all indicating statistically significant improvement. These changes reflect remolding of the stenosis, with regression toward a diffusely smaller artery than normal, and having less segmental narrowing and improved flow capacity.

Figure 5 summarizes these changes in which statistically significant changes were seen on the second arteriogram compared with those seen at the entry study.

Figure 6 shows dimensional changes in relation to adherence to the risk modification program for all patients in the combined control and treated groups classified according to severity of baseline stenosis at the ini-

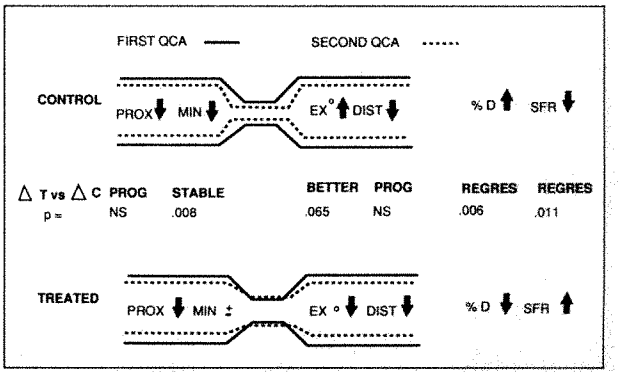


FIGURE 4. Comparison of stenosis dimensional changes (Δ) from initial (QCA, *solid line*) to follow-up (QCA, *dashed line*) arteriograms between control and treated groups.
ΔC = change in the control group; NS = not significant; REGRES = regression; ΔT = change in treated group; ± = no change; other abbreviations as in Figure 2.

tial entry study. For this analysis, the combined groups were divided into subgroups of poor adherence (adherence score of ≤0.75), good adherence (adherence score of >0.75 but ≤1.15) and those that excelled in risk factor management (adherence score of >1.15) where adherence measures were derived by dividing indexes of prescribed behavioral changes into the measured changes as described previously.[1]

Baseline mild lesions (stenosis flow reserve ≥3, Figure 6A) in the poor adherence group showed statistically significant progression of all dimensions, whereas groups with good and excellent adherence showed no progression. Baseline severe lesions (stenosis flow reserve <3, Figure 6B) in the poor and good adherence groups remained stable without further progression. Baseline severe stenoses in the group that excelled in

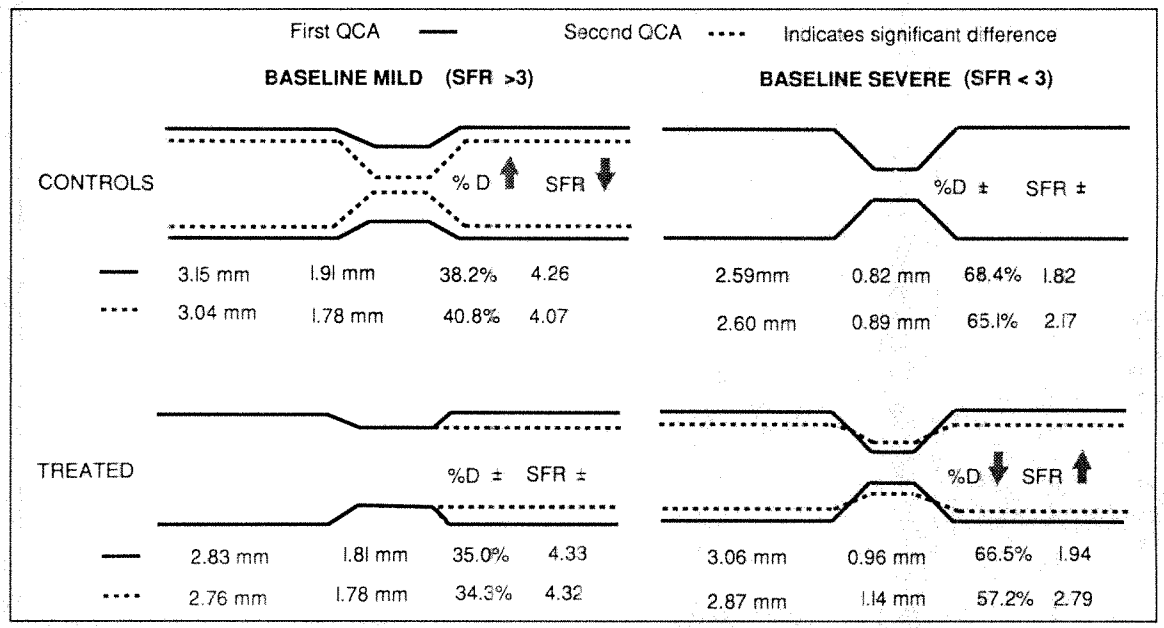


FIGURE 5. Stenosis change related to baseline severity in treated and control groups. Abbreviations as in Figure 2.

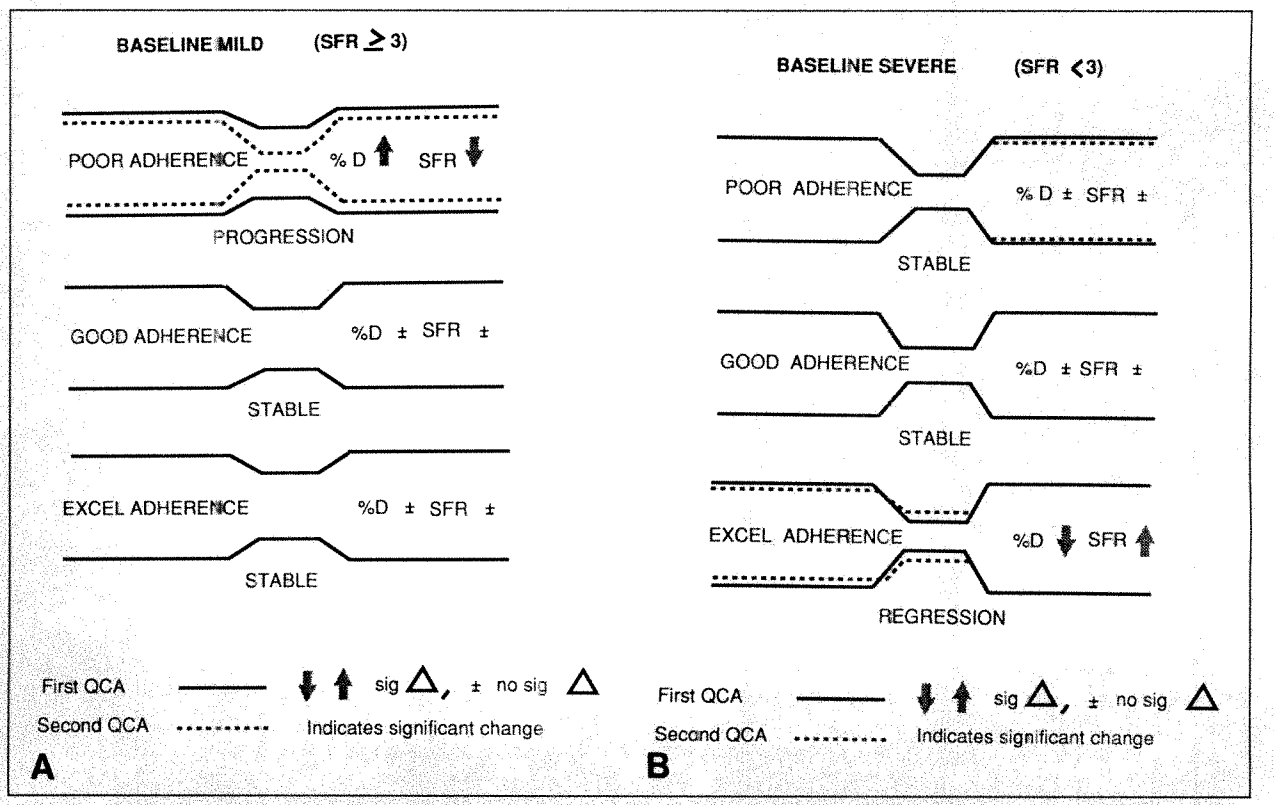


FIGURE 6. Stenosis change related to both baseline severity and adherence to the program of risk modification for mild baseline stenoses with stenosis flow reserve ≥3 *(A)* and for severe baseline stenoses with stenosis flow reserve <3 *(B)*. EXCEL = excellent; sig = significant; other abbreviations as in Figure 2.

TABLE IV Comparison of Methods, Sample Size, Outcome of Coronary Artery Disease Regression Trials

Study	End Points and Methods	No. of Subjects	p Value for End Point (Rx vs C)	End Points or End Point Change		% Δ Total Cholesterol (Rx-C)
				Control	Treated	
MRFIT[32]	Cardiac events, 1° prevention	12,866	NS	1.9%	1.8%	1.5%
Frick[33]	Cardiac events, 1° prevention	4,081	0.02	4.1%	2.7%	8.5%
CDP[34]	Cardiac events, 2° prevention	8,341	NS	26%	23%	10%
Carlson[35]	Cardiac events, 2° prevention	555	0.01	26%	17%	13%
CLAS[17]	Arteriog. score, visual estim.	162	0.001	0.5		22%
FATS[18]	% DS, visual borders	142	0.017	5.9% DS		29%
LHT[1,2]	% DS, automated	42	0.001	8.4% DS		20%
	Stenosis flow reserve		0.000	0.5		

For 1° and 2° prevention trials, end point = coronary artery disease events/no. of patients in each group; for arteriography end point = difference between controls (C) and treated group (Rx) in stenosis severity of study 1–study 2 of severe stenoses (> 50% DS or SFR > 3%).
Arteriog. = arteriography; CDP = Coronary Drug Project; % DS = % diameter narrowing of severe stenoses (> 50% or SFR > 3%); CLAS = Cholesterol-Lowering Atherosclerosis Study; estim. = estimated; FATS = Familial Atherosclerosis Treatment Study; LHT = Lifestyle Heart Trial; MRFIT = Multiple Risk Factor Intervention Trial; SFR = stenosis flow reserve.

adherence to the program showed statistically significant regression of minimal diameter, percent diameter stenosis and stenosis flow reserve. Therefore, good adherence to the lifestyle program prevented progression of milder stenoses, but more vigorous adherence was required for regression of severe coronary artery stenoses.

If the absolute dimension changes reported here are expressed as a percent change from baseline as in previous papers, the regression becomes even more apparent. For example, for severe baseline stenoses (stenosis flow reserve <3), the minimal diameter increased by a change of + 0.17 mm compared with a mean minimal absolute diameter of 0.96 mm at baseline, an approximately 18% improvement. In this same group, the percent diameter stenosis change was −9.3% stenosis diameter units from a mean baseline severity of 67% diameter narrowing, or a 14% improvement, with a t value of 4.05 and p value of 0.001. By comparison in this group, stenosis flow reserve improved by a change of + 0.85 over a baseline stenosis flow reserve at entry of 1.9, or a 45% improvement in stenosis flow reserve, with a larger t value of 5.11 and a p value of <0.0000. Therefore, the statistical significance of the changes in this study were greater for the integrated measure of severity than for the single measure of percent stenosis, although both showed significant improvement in the treated group.

Statistical analysis of stenoses as opposed to patients was performed because multiple stenoses in a patient showed changes essentially independent of each other as previously demonstrated.[1] Statistical analysis weighting for the small degree of within-patient-correlation of stenosis changes as previously described[1] did not change the significance of these results. Analysis was also performed on a per-patient basis by averaging all percent diameter stenoses for each patient and classifying patients according to threshold diameter stenosis unit changes of: ≥+10% for progression, ≤−10% for regression, and <±10% as no significant change, similar to Brown et al.[18] By this per patient analysis, 40% more of treated patients showed regression compared with control subjects, a statistically significant difference. However, we emphasize that this approach does not take into account the complex shape changes observed.

TABLE V Cholesterol and Coronary Artery Disease Regression in Arteriographic Trials

Study	Percent Change TC Rx–Control (%)	Arteriog. Reg.
Cohn[15]	6%	0
NHLBI[16]	17%	0
Nikkila[14]	18%	0
Nash[13]	18%	0
CLAS[17]	22%	16%
FATS[18]	29%	36%*
LHT[1,2]	20%	41%*

*Percentages of patients with > 10% diameter stenosis units of regression.
Arteriog. = arteriographic; Reg. = regression; Rx–Control = differences between treated and control groups; TC = total cholesterol; other abbreviations as in Table IV.

DISCUSSION

This study demonstrates that vigorous modification of multiple risk factors stops progression of mild to moderate coronary artery stenoses and causes regression of severe stenoses, leaving residual milder diffuse narrowing of the artery with less severe segmental stenoses and improved flow reserve. Complex shape changes or remolding of coronary stenoses occur with progression or regression so that no single anatomic dimension alone describes all of the geometric changes seen.

Significance of changes in stenosis shape: Although the number of patients in the study were small compared with previous reports, mean absolute changes of stenosis dimensions were statistically significant and internally consistent from several points of view. There was a dose effect of risk factor modification for preventing progression of mild stenoses and more stringent risk factor modification causing regression of severe stenoses. Severe stenoses showed greater regression than milder ones, reflecting a reasonable theoretical expectation that removal of a small amount of cholesterol from a severe stenosis having a small circumference would cause more improvement than the same amount of cholesterol removed from a mild stenosis having a large circumference. Published studies on experimental reversal report persistence of fibrosed, diffusely narrowed coronary arteries having less segmental narrowing in

treated groups compared with control subjects.[25–28] There are also different rates of progression/regression of different parts of atherosclerotic arteries in opposite directions depending on their histologic maturity and the duration/degree of serum/dietary cholesterol changes.[26–29] Finally, because coronary blood flow effects are a function of arterial radius raised to the fourth power, small changes in radius have proportionately much larger effects on the flow capacity and functional severity of stenoses, thus contributing to the greater significance of stenosis flow reserve as a measure of change in severity.

Comparison with other studies: Table IV compares representative primary and secondary intervention trials with the recent arteriographic randomized trials. In the spectrum of end point measures, from cardiac events to automated quantitative coronary arteriography for stenosis flow reserve, more quantitative or complete analysis of stenosis geometry, or both, yielded significant differences in end points with smaller numbers of subjects. Thus, the physiologic measure of severity (stenosis flow reserve accounting for the integrated total effects of all dimensional changes) shows statistical significance between treated and control groups with smaller numbers of study subjects than for other end points measured (Table IV).

Clinical implications: More stringent or vigorous treatment with lipid-lowering regimens[1,2,18] than conventionally used[30,31] appear necessary to achieve significant improvements in stenosis severity of treated versus control groups (Table V). The control groups of the most recent studies[1,17,18] following approximately the standard dietary guidelines of the American Heart Association[30] and National Cholesterol Education Program[31] showed high prevalence of progression.

Patients with coronary artery disease frequently have total cholesterol, and low- and high-density lipoprotein cholesterol levels that fall within the normal range, as were the average cholesterol levels in the Lifestyle Heart Trial.[1] However, in this study stringent dietary fat restriction and reduction of serum cholesterol substantially below "normal" levels were associated with the cessation of progression or regression of stenosis by quantitative coronary arteriography. The control group with average cholesterol levels within the normal range showed progression of coronary artery stenosis. Although not clearly defined, there may be a variable susceptibility to coronary atherosclerosis for given level of risk factor exposure and an important role of dietary fat separate from serum cholesterol. Many men with risk factors appear resistant to coronary artery disease despite risk factors or excess dietary fat, or both, whereas others are susceptible to even modest risk factors. In patients with coronary artery disease and normal cholesterol levels, vigorous reduction of dietary fat and reduction in cholesterol levels to substantially below "normal" ranges is associated with cessation of progression or regression of disease.

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Prediction by Postexercise Fluoro-18 Deoxyglucose Positron Emission Tomography of Improvement in Exercise Capacity After Revascularization

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The extent of ischemic and hibernating myocardium, which may be detected by increased postexercise uptake of fluoro-18 deoxyglucose (FDG) using positron emission tomography, may determine the degree of functional benefit after revascularization. This study examined the influence of the amount of this FDG-avid myocardium on changes in left ventricular function and exercise parameters after revascularization. Echocardiography and exercise testing were performed before and after intervention in 23 patients who had undergone positron emission tomography for the evaluation of myocardial perfusion (using rubidium-82), and postexercise FDG imaging in the fasting state. Follow-up echocardiography (22 ± 14 weeks after revascularization) was compared with preoperative FDG activity in 7 myocardial regions per patient.

Systolic function improved after intervention in 19 of 26 malperfused, dysfunctional FDG-avid regions (73%), and did not improve in 35 of 47 dysfunctional regions without increased FDG uptake (74%). The influence of the amount of FDG-avid tissue on changes in functional state was examined by comparing 9 patients with multiple (≥2) FDG-avid regions with the remainder. Those with multiple FDG-avid regions demonstrated improvement in peak rate-pressure product (20 ± 4 to 26 ± 4 × 10^3, p <0.02), and percentage of maximal heart rate achieved at peak (84 ± 10% to 93 ± 6%, p = 0.04), neither of which changed significantly in the remaining patients. Exercise capacity increased from 5.6 ± 2.7 to 7.5 ± 1.7 METS in the group with multiple FDG-avid regions; this increase of 55 ± 18% exceeded the increase of 13 ± 10% in the remainder (p = 0.04). Thus, imaging of postexercise FDG uptake in patients with previous myocardial infarction may predict improvement of regional systolic function and exercise parameters after revascularization.

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Myocardial revascularization is effective for the relief of angina, and thereby improves exercise parameters in some patients.[1,2] Likewise, in patients after myocardial infarction, recovery of regional left ventricular function may follow revascularization,[3–5] although changes of global ejection fraction are infrequent.[6–8] Improvements in either global ventricular function or exercise parameters after intervention probably reflect the number of viable but ischemic segments, which may benefit from a resumption of perfusion. Unfortunately, routine investigations have failed to identify viable myocardium reliably, which may be present in patients with wall motion abnormalities at rest, "non-reversible" perfusion defects or Q waves.[3–5,9,10] The use of positron emission tomography (PET) to examine uptake of the exogenous glucose tracer fluoro-18 deoxyglucose (FDG) has demonstrated viable tissue within areas subtended by Q waves, or showing perfusion and wall motion abnormalities.[11–13] In 2 studies examining postoperative follow-up in a total of 39 patients, metabolically active tissue was shown to regain regional function after intervention.[14,15] This study was designed to determine whether the combined extent of hibernating and transiently ischemic myocardium detected by FDG imaging could be used to predict the occurrence of functional benefits from revascularization.

METHODS

Patients: Patients with previous myocardial infarction and known coronary anatomy, in whom there was clinical uncertainty regarding the presence of ischemic or viable myocardium before myocardial revascularization, were eligible for the study. Past myocardial infarction was defined by the presence of electrocardiographic Q waves, with a wall motion abnormality and perfusion defect at rest. Patients with unstable angina pectoris, complex arrhythmias, and the usual contraindications to stress testing were excluded because of safety considerations. Subjects with fasting blood glucose levels >150 mg/100 ml were excluded because of potential difficulties in obtaining adequate metabolic imaging under these circumstances.

Study chronology: The protocol was performed after obtaining informed consent. Patients were studied after an overnight fast, and antianginal therapy was withheld on the day of the test. Before intervention, regional wall motion analysis was assessed using 2-dimensional echo-

cardiography, myocardial perfusion was evaluated using dipyridamole stress rubidium (Rb)-82 PET, and patients underwent symptom-limited maximal exercise, with postexercise FDG imaging. Echocardiography and exercise testing were repeated in patients in whom complete revascularization was achieved.

Digitized two-dimensional echocardiography: Standard equipment was used to acquire 2-dimensional echocardiograms, using parasternal long- and short-axis, and apical 4- and 2-chamber views. Images were digitized on-line (PreVue, Nova Microsonics, Indianapolis, Indiana), and recorded in a cine-loop format. Images before and after revascularization were then displayed side by side in a quad-screen display, to facilitate comparison of regional motion in 7 myocardial regions (anteroseptal, septal, anterior, lateral, posterior, inferior and apical) corresponding to those used for interpretation of PET images. Left ventricular ejection fraction was calculated using single-plane Simpson's rule.[16] Wall motion was scored by 2 experienced echocardiographers unaware of the scintigraphic and exercise data, using a conventional wall motion score[17]: 1 = normal wall motion, 2 = hypokinesia, 3 = akinesia, 4 = dyskinesia, 5 = aneurysm, and 6 = akinesia or dyskinesia with thinning of the myocardium. Hibernation was defined by functional improvement (e.g., dyskinesia to hypokinesia, akinesia to normal) within each individual segment.

Exercise stress testing: Because of the variability in exercise tolerence between patients of different ages with various degrees of left ventricular impairment, maximal treadmill exercise testing was performed using a protocol chosen in accordance with each patient's exercise capacity. Conventional clinical and electrocardiographic monitoring was used during the test, with the usual end points to guide the completion of the procedure.[18] The presence of >1 mV horizontal or downsloping ST-segment depression was considered indicative of ischemia. The peak heart rate–systolic blood pressure product, peak heart rate (expressed as a percentage of age-predicted maximal heart rate), and estimated work load[19] were recorded for each test.

Positron emission tomography: Images were acquired with a Posicam system (Positron Corporation, Houston, Texas), in 21 slices of 5 mm thickness using a 256 × 256 matrix. Fluoroscopic localization of the inferior cardiac border was used to assist the positioning of patients in the PET scanner. A transmission scan was performed using a gallium-68–filled Plexiglas® ring. The same attenuation correction data were applied to both the perfusion and FDG images, followed by back projection (with a Butterworth filter order 5, cutoff 0.4) and image processing and display. Images were displayed using a quantitative color scale in tomographic views as well as a polar map display. Perfusion and metabolic activity were interpreted in 7 myocardial regions to permit comparison of equivalent areas with 2-dimensional echocardiographic interpretation.

Myocardial perfusion imaging: The perfusion images used in this study followed a previously described protocol,[20] involving a bolus injection of 40 to 60 mCi of Rb-82 at rest and after a standard intravenous dipyridamole-handgrip stress,[21] during which patients were continuously monitored clinically and electrocardiographically. Perfusion imaging was interpreted in accordance with criteria established in a previous series of approximately 200 patients[20] into normal, ischemic or infarcted tissue. Normal perfusion was defined by Rb-82 activity within 20% of the maximum for the study. Ischemia was diagnosed if a segment showed a relative reduction in activity of >20% in relation to the maximal counts after dipyridamole stress. Infarction was identified by a fixed perfusion defect (>20% below maximal counts on the resting images).

Myocardial metabolic imaging: Metabolic imaging was performed after exercise in the fasting state,[22,23] without antianginal medications for 24 hours. Patients underwent treadmill exercise (as previously described), and 5 to 10 mCi of FDG were injected 30 minutes after exercise; this delay was selected in light of previous data,[22] to ensure the return of nonischemic tissue to normal FDG uptake. PET images were acquired after a 40-minute delay to allow for achievement of myocardial uptake and phosphorylation. By orientation of the patient in the scanner using skin markings obtained during the initial fluoroscopic localization of the heart, the same patient-positioning was obtained for both PET studies. Thus, location of the heart in the perfusion images could be used to assist with orientation of the FDG images if the FDG activity in normal myocardium was too low to adequately outline the heart. Equivalent myocardial segments were therefore portrayed in the same location on both Rb-82 and FDG images.

The same 7 segments used for perfusion imaging were used by 2 blinded observers to estimate regional FDG activity. A "reference normal" segment for FDG activity was defined for each patient in the region of maximal Rb activity at rest, supplied by a normal coronary artery and without significant reduction of relative Rb activity after dipyridamole stress. Other sites with submaximal Rb activity at rest (but still in the normal range), without significant alteration after dipyridamole stress and supplied by normal coronary arteries, were then combined to establish a range of normal FDG uptake, measured as a percentage below or above the reference level. Thus, in each patient, abnormal metabolic activity was defined by FDG activity >2 standard deviations (≥30%) above the reference normal segment. Metabolic evidence of ischemia was identified by FDG avidity in the presence of normal perfusion at rest. Within areas of abnormal regional wall motion, viable regions were identified by avid FDG uptake despite hypoperfusion at rest, and nonviable myocardium was identified by FDG activity less than or equal to normal.

Data analysis: Improvement of regional function at follow-up echocardiography was used as the "gold standard" to evaluate the efficacy of postexercise FDG imaging for predicting myocardial viability. The numbers of regions with and without functional recovery were related to the presence or absence of increased regional FDG uptake to yield predictive values of positive and negative test results. In addition, influence of the ischemic burden on functional improvement was assessed by comparison of left ventricular function and exercise parameters before and after revascularization in pa-

tients with ≥2 FDG avid regions, and those with 1 or no such regions.

RESULTS

Patient characteristics: Preoperative evaluation, full revascularization, and the appropriate follow-up were completed in 23 patients between June 1989 and March 1991: mean age was 58 ± 9 years and 11 were men. All had had a previous Q-wave myocardial infarction; preoperative studies were performed ≥2 weeks (mean 14 ± 40) after this event. Five patients (22%) were in New York Heart Association functional class III; 11 (48%) were in class II, and the remaining 7 had normal functional status. Twelve patients had multivessel disease, and the mean preoperative ejection fraction was 0.35 ± 0.14. Revascularization was indicated for the control of ischemic symptoms (n = 8) or on prognostic grounds; 12 underwent coronary angioplasty and 11 required bypass surgery. Follow-up echocardiography and exercise testing were performed 22 ± 14 weeks later.

Preoperative prediction of myocardial viability: Abnormal regional wall motion was demonstrated in 100 regions at preoperative echocardiography, including 46 with hypokinesia and 54 with akinesia or dyskinesia. The mean blood flow at rest in hypokinetic segments was 58 ± 10% of maximum, compared with 55 ± 11% in akinetic segments (p = not significant [NS]). To avoid inappropriate inclusion of normal regions showing mild nonspecific hypokinesia or with abnormal wall motion due to peri-infarct tethering, the response of dysfunctional regions to revascularization was only considered when a matching perfusion defect was apparent at Rb-82 PET imaging. Of these 73 regions with both regional dysfunction and malperfusion at rest, only 4 showed a significant further reduction of perfusion after dipyridamole therapy.

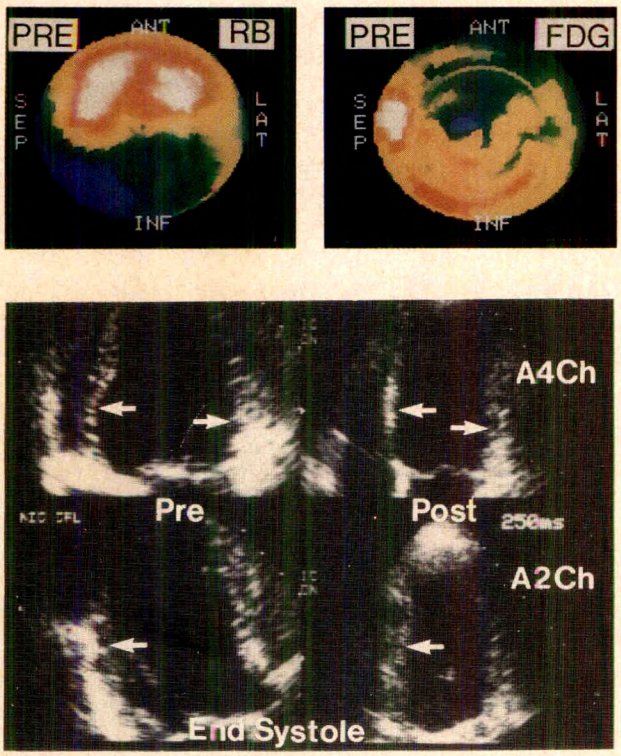


FIGURE 1. Functional improvement in multiple fluoro-18 deoxyglucose (FDG)-avid regions. Polar maps *(top)* display preoperative perfusion (PRE RB) and metabolic (PRE FDG) images, showing a large inferolateral (LAT), inferior (INF) and septal (SEP) perfusion defect, corresponding to the site of increased FDG uptake (note that the normally perfused anterior (ANT) wall shows low FDG activity). End-systolic echocardiographic images in 4- and 2-chamber (Ch) views *(bottom)* show impaired contraction in the septal, lateral and inferior walls preoperatively, which recover function postoperatively.

Preoperatively, 19 patients had a total of 30 regions with increased regional postexercise FDG activity. Of these 30 FDG-avid regions, 4 had normal function and perfusion (corresponding to ischemic tissue), whereas 26 (in 16 patients) were within dysfunctional sites. The latter were in the anterior, anteroseptal, septal or apical regions in 14, lateral or posterior regions in 6, and the inferior region in 6 segments. Preoperative metabolic imaging thus predicted the presence of some viable myocardium in 70% of the 23 patients, and in 36% of the 73 regions with both perfusion and functional abnormalities after myocardial infarction. Regions with increased FDG uptake showed no significant difference in Rb-82 activity at rest (60 ± 8% of maximum) from the remaining regions (55 ± 11%, p = NS). Segments with Rb activity ≤50% of maximum were present in 5 of 26 FDG-avid sites (19%), and in 19 of the remaining 47 sites (40%, p = NS).

Regional left ventricular function: Of the 16 patients with FDG-avid tissue at preoperative PET, 13 showed improved regional function after revascularization (81% predictive value of a positive result on a patient basis). Conversely, 7 patients lacked increased FDG uptake, 5 of whom showed no improvement in left ventricular function (71% predictive value of a negative result on a patient basis). Echocardiographic regional wall motion improved in 15 patients, 13 of whom were predicted to improve by preoperative FDG imaging (sensitivity 87%). Failure to improve left ventricular function occurred in 8 patients, 5 of whom were predicted not to improve by preoperative FDG imaging (specificity 63%).

Regional contractility improved after revascularization in 19 of the 26 FDG-avid dysfunctional segments (73% predictive value of a positive result on a segmental basis). Thirty-five of the 47 dysfunctional regions without increased FDG uptake failed to improve (74% predictive value of a negative result on a segmental basis). Thus, 31 of the 73 dysfunctional, malperfused regions (42%) improved function after operation. This recovery was by >2 points (e.g., normalization of preoperative akinesia, or dyskinesia improving to hypokinesia) in 9 regions, 7 (78%) of which were FDG-avid. In myocardium showing recovery of regional function after revascularization, the preoperative Rb-82 level at rest was 60 ± 10% of maximum, compared with 55 ± 11% in nonviable tissue (p = NS). Regional Rb-82 activity ≤50% at rest was present in 8 of the 31 viable segments (19%) and in 19 of the 47 nonviable regions (40%, p = NS).

TABLE I Comparison of Pre- and Postoperative Left Ventricular Function and Exercise Parameters in Patients with ≥2 Fluoro-18 Deoxyglucose Positive Regions to Those with ≤1 Region

	FDG ≥2 Regions (n = 9)			FDG ≤1 Region (n = 15)		
	Before	After	p Value	Before	After	p Value
WM score (all LV)	2.1 ± 0.4	1.5 ± 0.4	0.01	2.0 ± 0.5	1.9 ± 0.5	NS
WM score (MI seg.)	2.7 ± 0.4	1.7 ± 0.6	0.01	2.8 ± 0.6	2.5 ± 0.9	NS
Ejection fraction	37 ± 11	40 ± 9	NS	38 ± 13	38 ± 13	NS
Peak HR (% max)	84 ± 10	93 ± 6	0.04	85 ± 10	87 ± 11	NS
Peak HR·BP ($\times 10^3$)	20.4 ± 4.4	25.5 ± 3.6	0.02	20.0 ± 5.0	23.2 ± 3.7	NS
Exercise capacity (METS)	5.6 ± 2.7	7.5 ± 1.7	0.08	6.5 ± 2.8	8.2 ± 2.2	NS
ST depression >1 mm	1	0	NS	3	0	NS

BP = blood-pressure; FDG = fluoro-18 deoxyglucose; HR = heart rate; LV = left ventricular; METS = multiples of resting oxygen consumption (estimated); MI = myocardial infarction; NS = not significant; seg. = segment; WM = wall motion.

Global left ventricular function: Multiple (≥2) FDG+ sites were present in 9 of the 19 patients with FDG-avid regions (Figure 1). This group was compared with the remaining patients (Table I) in order to examine the functional benefits of revascularizing a substantial ischemic burden (approximately 30% of the left ventricle). Patients with multiple FDG-avid sites had significant improvement in both the mean wall motion score index for the left ventricle (2.1 ± 0.4 to 1.5 ± 0.4, $p < 0.01$) and the mean wall motion score in the dysfunctional segments (2.7 ± 0.4 to 1.7 ± 0.6, $p < 0.01$); these changes were less marked in the remaining patients (Table I). Ejection fraction in patients with multiple FDG-avid sites increased from 37 ± 11 to 40 ± 9, but this change was not significant; no change was apparent in the remaining patients.

Functional class: Before intervention, 3 of the 9 patients with multiple FDG-avid regions were in New York Heart Association functional class III, and 4 were in functional class II, compared with 2 and 7 of the remaining 14 patients, respectively. Postoperatively, 5 of the patients with multiple FDG-avid regions improved, and 4 were unchanged. Of the remaining patients, 3 improved, 9 were unchanged and 2 deteriorated.

Exercise parameters: All patients underwent exercise testing before revascularization; patients with and without multiple FDG-avid regions did not differ significantly with respect to exercise parameters preoperatively. One of the 9 patients (11%) of the group with multiple FDG-avid regions, and 3 of the remaining 15 patients (20%, p = NS) had their preoperative exercise capacity limited by ischemia.

Postoperatively, all patients were able to exercise in the group with multiple regions of increased FDG uptake in the preintervention PET study, but in the remaining group 2 patients were unable to exercise because of heart failure, and 1 because of musculoskeletal problems. After revascularization, no exercise tests were limited by ischemia in either group. Despite their preoperative similarities, exercise parameters improved in patients with multiple FDG+ regions, but not in the remainder (Figure 2). The percentage of peak-predicted maximal heart rate increased from 84 ± 10 to 93 ± 6

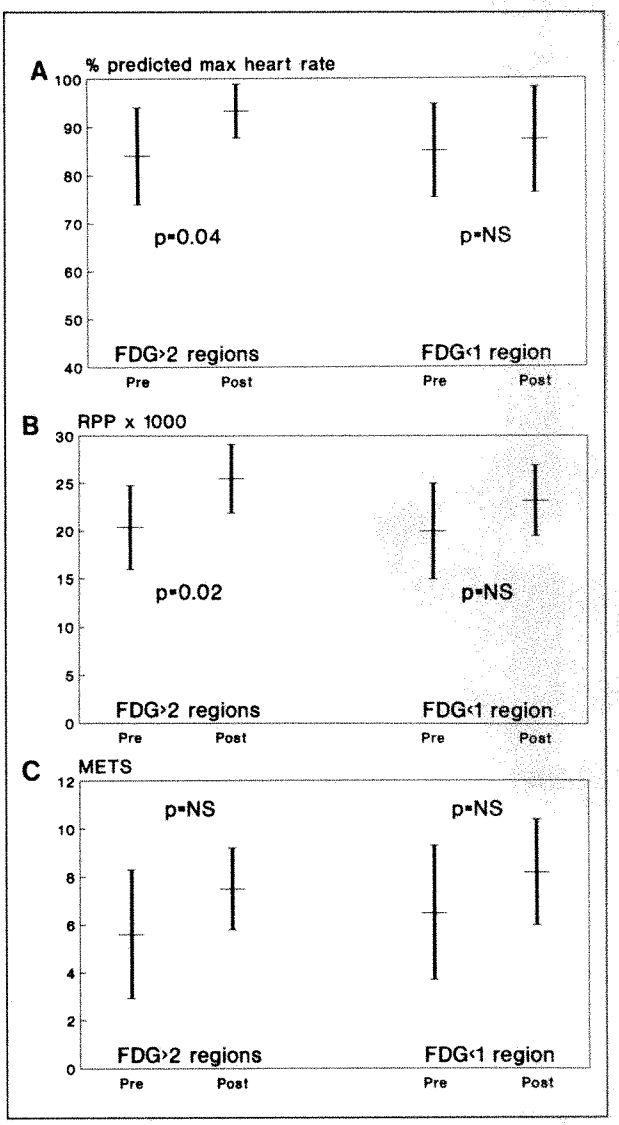


FIGURE 2. Comparison of groups with multiple fluoro-18 deoxyglucose (FDG)-avid and ≤1 FDG-avid region, with respect to pre- and postoperative heart rate *(A)*, rate-pressure product (RPP) *(B)* and estimated exercise capacity *(C)*. max = maximal; METS = multiples of resting oxygen consumption (estimated); NS = not significant.

postoperatively ($p = 0.04$) in the group with multiple FDG-avid segments compared with no significant change in the remainder. The peak product of heart rate and blood pressure increased from $20.4 \pm 4.0 \times 10^3$ to $25.5 \pm 3.6 \times 10^3$ ($p = 0.02$) in the multiple FDG-avid group, also with no significant change in the remaining patients. There was an increase in estimated exercise capacity from 5.6 ± 2.7 to 7.5 ± 1.7 in patients with multiple FDG-avid regions; although this was not statistically significant, the latter group demonstrated a significantly greater improvement than did the remaining group ($55 \pm 18\%$ vs $13 \pm 10\%$, $p = 0.04$).

DISCUSSION

This study suggests that, in patients who undergo revascularization after myocardial infarction, improvements of ventricular function and exercise capacity may be predicted by postexercise PET imaging of FDG uptake in the fasting state.

Methodologic considerations: The population under study was selected to include patients in whom the data would be clinically pertinent; these subjects did not have extensive evidence of ischemia by conventional criteria. Similarly, we limited the segmental analysis to regions where there was no evidence of viability by conventional criteria; postinfarction segments analyzed for the presence of viability had both a perfusion and a wall motion disturbance. This prevented dilution of the regional analysis by normal regions tethered to scars, and avoided the inclusion of regions with nonspecific hypokinesia. Similarly, regional analysis was based on 7 regions to ensure that substantial regions of myocardium were examined, as well as to permit comparisons with previous studies using similar criteria at nuclear ventriculography.

This study used imaging of myocardial FDG uptake in the fasting, postexercise state, when FDG "hotspots" reflect the persistence of increased glucose uptake in postischemic tissue, at a time when normal myocardium has returned to normal resting perfusion and low glucose utilization.[24] The low FDG activity of normal myocardium may lead to some ambiguity in the delineation of the myocardial border on the FDG images, but we attempted to circumvent this problem by using perfusion images to guide the orientation of FDG images during processing. The fasting FDG protocol permitted detection of ischemic as well as hibernating tissue, facilitating quantitation of the amount of myocardium that might benefit from revascularization. This approach contrasts with the usual technique of FDG imaging after the ingestion of a glucose load, which enhances FDG uptake of all viable myocardium. The glucose loading technique permits hibernating tissue to be identified by the presence of a "metabolism-perfusion mismatch,"[25] but does not identify ischemic myocardium, which may contribute to exercise intolerance.

Prediction of myocardial viability: In this study, no relation was apparent between the degree of preintervention wall motion abnormality, or the severity of malperfusion, and viability. These data are consistent with previous studies showing conventional indexes of viability[3–5,9–13] to be poorly predictive of functional recovery. However, studies using PET with Oxygen-15 water have suggested that absolute myocardial perfusion at rest may be predictive of myocardial viability.[26] The failure of Rb-82 activity to reproduce the latter findings reflects the use of a more qualitative approach to flow with static imaging in this study.

Metabolic activity has previously been demonstrated in areas otherwise believed to be infarcted,[7–9] but only 2 studies (involving 39 patients) have examined the effect of revascularization of such regions on regional left ventricular function. Tillisch et al[14] examined regional FDG uptake after glucose loading, and compared the prediction of viability with changes in regional wall motion in 7 segments per patient using nuclear and contrast ventriculography. Thirteen of 16 regions with FDG activity within hypoperfused, dysfunctional segments improved function postoperatively (predictive value for a positive test, 81%). Significant improvement in ejection fraction was reported in patients with ≥ 3 viable regions. Conversely, FDG criteria for nonviability predicted failure to improve function in 24 of 26 areas (a 92% predictive value for a negative test). FDG imaging in the fasting state was used by Tamaki et al[15] in a study of otherwise similar design. Of 23 revascularized segments showing preoperative asynergy, 16 improved function (predictive value for a positive test, 78%), but no changes in global ejection fraction were reported. Of 23 similar segments without FDG activity, 18 were unchanged functionally after revascularization (predictive value for a negative test, 78%).

With respect to changes in regional left ventricular function, the results of this study most resemble those of Tamaki et al, reflecting the use of fasting imaging for both studies. The fasting PET technique is associated with the detection of regions, which despite FDG avidity, fail to improve after revascularization, reducing the predictive accuracy of positive test results. Some of these "false-positives" may reflect regional heterogeneity in the FDG uptake of normal fasting myocardium.[27,28] However, this phenomenon is unlikely to be the major factor underlying the false-positive rate because such hotspots are generally seen in the posterolateral wall, which was not the predominant site of false-positive FDG results in this study. Two alternative explanations may account for the failure of FDG-avid regions to improve function, without being truly false-positive. First, some patients may not have achieved full revascularization at the time of follow-up because of restenosis after angioplasty or because of bypass graft closure (both processes would account for failure to improve regional function). Second, a small quantity of ischemic tissue may produce a positive fasting FDG signal, but not be extensive enough to produce an improvement in regional function. In contrast, FDG-avid regions using glucose-loaded FDG protocols show greater specificity with respect to the identification of sufficient viable tissue to produce an improvement of regional function at rest.

Selection of postinfarction patients for revascularization: Whereas preoperative PET metabolic imaging may predict the probability of improved regional myocardial function, the referral of postinfarction patients

for revascularization would be more attractive if functional improvement could be predicted. This is because the chief prognostic determinants in these patients are global left ventricular function[29] and exercise capacity,[30,31] the impairment of which reflects the failure of ischemic or hibernating myocardium to contribute to contractile reserve. Revascularization of such areas would reverse their functional insufficiency, with consequent benefits on exercise capacity if the quantity of hibernating and ischemic tissue were extensive enough. The postexercise FDG method used in this study is able to assess the amounts of both hibernating and transiently ischemic tissue, both of which are characterized by FDG avidity. The results of this study are consistent with this reasoning: revascularization in patients with multiple regions of FDG-avidity at postexercise imaging in the fasting state is associated with an improvement in exercise parameters, including a greater peak exercise heart rate and rate-pressure product, and a greater increase in exercise capacity. Such improvements occurred in the absence of significant enhancement of global ejection fraction at rest—a pattern consistent with previous findings[7,8]—probably reflecting a reduction in compensatory hyperkinesia in uninvolved areas following the recovery of viable regions.

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Implications of Inferior ST-Segment Elevation Accompanying Anterior Wall Acute Myocardial Infarction for the Angiographic Morphology of the Left Anterior Descending Coronary Artery Morphology and Site of Occlusion

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Inferior ST-segment elevation during anterior wall acute myocardial infarction (AMI) due to left anterior descending (LAD) coronary artery occlusion is unusual and was not previously investigated. This study tested the hypothesis that inferior ST-segment elevation during anterior AMI predicts a specific angiographic morphology that satisfies 2 necessary conditions: (1) mass of ischemic anterior wall myocardium is relatively small, resulting in a weaker anterior injury current and less reciprocal inferior ST-segment depression; and (2) there is concomitant inferior wall transmural ischemia that further shifts the inferior ST segments upward.

The study group consisted of 42 consecutive patients with anterior AMI undergoing angiography at 4.1 days (range 0 to 14). Coronary angiograms were examined for 3 features: (1) site of LAD artery occlusion (a distal obstruction implying a smaller mass of ischemic anterior wall myocardium), (2) LAD artery extension onto inferior wall of left ventricle (termed a "wrap around" vessel), and (3) collateral flow from LAD artery to inferior wall. The latter 2 features would be expected to contribute to inferior wall transmural ischemia.

Acute inferior ST-segment elevation (sum of ST-segment deviation in leads II, III and aVF $\geq$3.0 mm) was seen in 7 patients (16%). A greater number of LAD artery branches proximal to the site of occlusion was significantly correlated with less inferior ST-segment depression ($r = 0.59$, $p < 0.01$). The 33 patients with an LAD artery that "wrapped around" the cardiac apex to the inferior wall had less total inferior ST-segment depression than that of the 9 with a shorter artery (0.2 ± 4.0 vs -3.0 ± 2.8 mm; $p < 0.05$). Of the 7 patients with inferior ST-segment elevation, 5 had a wrap around artery with the culprit lesion distal to 3 major branches. This combination of angiographic findings occurred in only 2 of the other 35 patients (odds ratio 44, 95% confidence interval 4 to 632; $p < 0.001$). These results support the hypothesis that inferior ST-segment elevation during anterior AMI results from a smaller mass of ischemic anterior myocardium combined with simultaneous inferior transmural ischemia (i.e., a distal occlusion in a wrap around LAD coronary artery).

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The hallmark of transmural acute myocardial infarction (AMI) is ST-segment elevation on the body surface electrocardiogram. This is often accompanied by reciprocal ST-segment depression in leads oriented opposite to those displaying ST-segment elevation.[1] Reciprocal ST-segment depression is believed to occur because of the orientation of the 2 groups of electrocardiographic leads to the injury current dipole and may be further influenced by the presence of myocardial ischemia in areas remote from that undergoing AMI.[2] Whereas reciprocal inferior ST-segment depression has been extensively studied, little information exists concerning the incidence, cause and clinical significance of simultaneous anterior and inferior ST-segment elevation in the setting of anterior AMI (termed "anterior-inferior" AMI).[3–6] In one study it was shown that when $\geq$25% of the inferior wall of the left ventricle was supplied by the left anterior descending (LAD) coronary artery (either directly or by collateral flow) there was significantly less acute inferior ST-segment depression.[3] It was reasoned that this anatomic feature caused simultaneous inferior wall transmural ischemia, producing an injury current directed toward leads II, III and aVF, which attenuated the reciprocal ST-segment depression caused by the anterior wall injury current.

To further explain the cause of the anterior-inferior AMI pattern, we propose that a second condition is necessary in addition to the occurrence of transmural ischemia in part of the inferior wall. This condition is that the occlusion of the LAD coronary artery be located in the distal vessel. This results in a smaller mass of ischemic anterior wall myocardium that in turn generates a weaker anteriorly directed injury current and less reciprocal ST-segment depression, allowing the inferior ST segments to move further upward. It is the combination

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of these 2 circumstances that permits frank inferior ST-segment elevation to become manifest. Therefore, the purpose of this study was to: (1) determine the incidence of the anterior-inferior AMI electrocardiographic pattern, and (2) test the hypothesis that this distinctive electrocardiogram predicts a specific angiographic morphology—distal occlusion of an LAD coronary artery that extends around the apex to supply part of the inferior wall.

METHODS

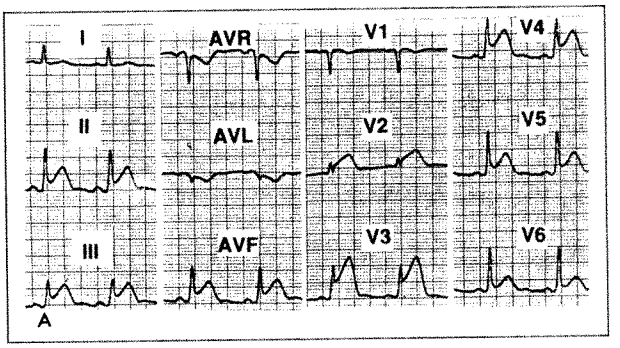
Patient selection: From a review of the cardiac catheterization laboratory records at the University of North Carolina Hospital between November 1988 and November 1990 we identified 70 consecutive patients undergoing cardiac catheterization within 14 days of an anterior AMI or an episode of prolonged transmural anterior myocardial ischemia. Anterior AMI was defined by (1) ischemic chest pain of ≥2-hour duration, (2) ST-segment elevation ≥2 mm (1 mm = 0.1 mv) in ≥3 of leads V_2–V_5 of a standard 12-lead electrocardiogram, and (3) subsequent elevation in the creatine phosphokinase-MB isoenzyme. Patients (n = 3) meeting the first 2 criteria, but without subsequent enzyme elevations were considered to have had prolonged transmural ischemia without AMI. They were included in the study group, because it was thought that their acute electrocardiograms reflected the same pathophysiology as those of subjects who had subsequent enzyme elevations.

All medical records were reviewed to obtain an electrocardiogram performed within 6 hours of the onset of chest pain and within 2 hours of the initiation of thrombolytic therapy or before percutaneous transluminal coronary angioplasty. In 20 patients who had been transferred from other hospitals, an appropriately timed electrocardiogram was not available, and they were excluded. Other reasons for exclusion included bundle branch block (n = 3), inability to fully visualize the terminal LAD coronary artery (n = 3), and a non-LAD artery infarct (occlusion of diagonal or ramus intermedius branches; n = 2). The remaining 42 patients constituted the study group.

Analysis of electrocardiograms: In patients with >1 available tracing, the one with the greatest magnitude of precordial ST-segment elevation was analyzed. The magnitude of ST-segment deviation relative to the TP segment in each of the 12 standard leads was measured to the nearest 0.5 mm at 80 ms after the J point. Measurements obtained by 2 independent observers unaware of all clinical and angiographic information were averaged for each lead. Inferior lead ST-segment deviation was expressed as the sum of ST-segment deviation in leads II, III and aVF, with a positive value representing net ST elevation, and a negative one, net ST-segment depression.

The anterior-inferior AMI pattern was defined as predominantly anterior precordial lead ST-segment elevation accompanied by summed ST-segment elevation in leads II, III and aVF of ≥3 mm. This definition was chosen because the mean of 1 mm of ST-segment elevation in each inferior lead is consistent with generally accepted electrocardiographic criteria signifying inferior wall transmural ischemia (Figure 1A).

Analysis of coronary angiograms: Coronary angiograms were read in a consensus fashion by 2 investigators unaware of the electrocardiographic findings. Multiple projections of the LAD coronary artery were examined for 3 features. First, the LAD artery was classified as terminating at the cardiac apex or as extending around the apex to supply part of the inferior wall. The cardiac apex was defined in the lateral view by the point at which the artery assumed a course perpendicular to the midportion of the vessel. A vessel extending beyond the apex to an arbitrarily determined point on the inferior apex was termed a wrap around artery (Figure 1B). This dichotomizing point was assessed visually, but represents a true distance of approximately 1.7 cm, determined by comparison with angiographic catheter diameter in the same frame. In 6 patients with totally occluded LAD arteries, this feature was assessed by collateral flow to the vessel. Second,



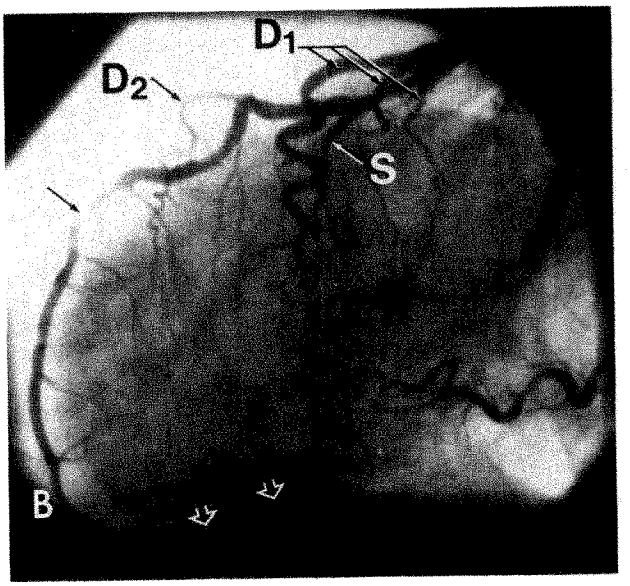


FIGURE 1. ***A*, electrocardiogram of patient with acute anterior myocardial infarction showing characteristic precordial lead ST-segment changes, as well as inferior lead ST-segment elevation ("anterior–inferior" myocardial infarction). *B*, lateral projection of left anterior descending coronary artery in same patient 3 days after infarction. *Unlabeled solid arrow* indicates distal subtotal occlusion. *Double open arrows* indicate terminal portion of vessel on inferior wall of left ventricle. In this case, angiographic score (see text) is 4. D_1 = branching first diagonal vessel; D_2 = second diagonal vessel; S = first septal perforating artery.**

the number of patent branches of the LAD artery, which originated proximal to the lesion responsible for the infarct, was enumerated. There were 4 important branches considered: (1) ramus intermedius (if present), (2) first large septal perforating vessel, (3) first diagonal vessel and (4) second diagonal vessel. The site of the infarct-related lesion was determined by the location of a total occlusion or by the stenosis with the greatest reduction in luminal diameter by visual estimate. Finally, collateral flow from the LAD coronary artery to the inferior wall, which originated distal to the culprit lesion, was classified as present or absent.

Angiographic score: An angiographic scoring system was devised for the purpose of evaluating the 3 angiographic features proposed to cause the anterior-inferior AMI pattern. The scoring system was designed so that a low score was associated with the angiographic features predicted to cause more inferior ST-segment depression, and a higher score with those predicted to cause inferior ST-segment elevation.

MASS OF ISCHEMIC ANTERIOR WALL MYOCARDIUM: It was reasoned that if the site of occlusion in the LAD artery was located distally there would be more proximal branch vessels patent to perfuse the anterior wall, and thus a lesser volume of ischemic anterior wall myocardium. This would generate a smaller anterior wall injury current and less reciprocal inferior ST-segment depression. Therefore, 1 point was allowed for each important branch of the LAD artery proximal to the site of occlusion, to a maximum of 3 points. A score assigning only ½ point per vessel was also tested.

LEFT ANTERIOR DESCENDING CORONARY ARTERY EXTENDING ONTO THE INFERIOR WALL: Occlusion of a wrap around LAD artery could result in some inferior wall transmural ischemia and attenuate the reciprocal ST-segment depression expected to result from anterior wall transmural ischemia. Therefore, 1 point was given for a wrap around LAD coronary artery that supplied part of the inferior wall.

COLLATERAL FLOW FROM THE LEFT ANTERIOR DESCENDING CORONARY ARTERY TO THE INFERIOR WALL: If the inferior wall was supplied by collaterals from the LAD coronary artery, 1 point was given. In this case, an LAD coronary artery occlusion would be more likely to produce inferior wall transmural ischemia, thereby shifting the inferior lead ST segment upward. The scoring system is depicted graphically in Figure 2.

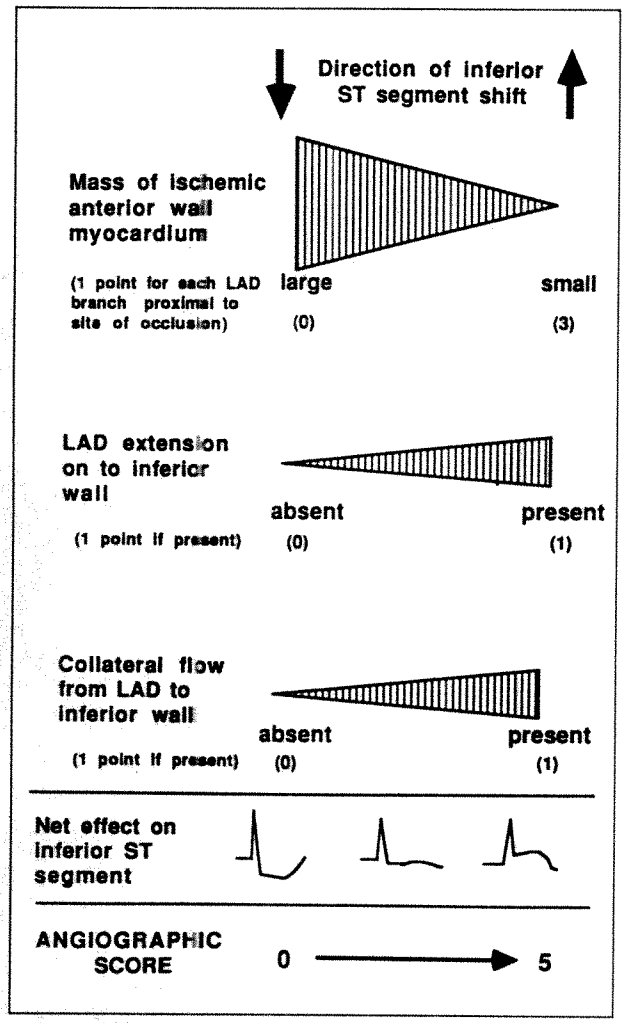


FIGURE 2. Derivation of angiographic score. Each of 3 angiographic features postulated to influence inferior ST segment are shown, with magnitude of effect on inferior ST segment represented graphically. Mass of ischemic myocardium was postulated to be inversely related to number of branches proximal to site of left anterior descending (LAD) occlusion, and 1 point was given for each proximal branch (maximum 3 points). One point was given for LAD that supplied part of inferior wall, and 1 point for LAD that supplied collateral flow to inferior wall.

Statistical analysis: Data are expressed as mean ± 1 standard deviation. The relation between continuous and noncontinuous variables was assessed by the Spearman rank-order correlation method. Linear regression was used to compare 2 continuous variables, and the differences between 2 groups of continuous variables were assessed by a 2-tailed Student's t test. The independent contribution of LAD artery extension to inferior ST-segment deviation was assessed by converting the number of vessels proximal to the site of occlusion to a categorical variable and then performing multiple variable regression. The occurrence of the anterior-inferior AMI pattern and its relation to angiographic morphology were evaluated by a chi-square analysis and Fisher exact test. A p value <0.05 was considered significant.

RESULTS

Patient characteristics: The study group consisted of 33 men and 9 women (mean age 57 ± 12 years). There was history of AMI in 7 patients (inferior, n = 2; anterior, n = 1; non-Q-wave, n = 1; and indeterminate, n = 3). Patients underwent cardiac catheterization and coronary angiography a mean of 4.1 ± 3.7 days after AMI. In all but 1 patient, the residual stenosis of the lesion thought responsible for the AMI was ≥50%. This patient was included in the study because the stenosis (30%) was the only coronary artery lesion identified.[7] Mean left ventricular ejection fraction was 0.49 ± 0.13 (range 0.23 to 0.72), with anterior wall segmental dys-

function noted in 33 of 35 patients undergoing left ventriculography.

"Anterior-inferior" myocardial infarction: An anterior-inferior AMI pattern was present in 7 of 42 patients (16%), and in these there was a significantly greater incidence of a specific LAD coronary artery angiographic morphology. The combination of an LAD artery occlusion located beyond 3 major branches in a vessel that "wrapped around" the cardiac apex to supply part of the inferior wall of the left ventricle, was seen in 5 of 7 patients with the electrocardiographic pattern of anterior-inferior AMI. In contrast, only 2 of 35 patients without this electrocardiographic pattern had both angiographic features (odds ratio 44, 95% confidence interval 4 to 632; $p < 0.001$). The other 2 patients with anterior-inferior AMI electrocardiograms had wrap around LAD arteries with 2 patent vessels proximal to the occlusion. Patients with and without the anterior-inferior AMI electrocardiogram had similar values for the sum of ST-segment elevation in leads V_2–V_6, I and aVL (19 ± 5 vs 20 ± 13 mm).

Factors influencing inferior ST-segment deviation: There was a significant relation ($r = 0.58$; $p < 0.01$) between angiographic score and sum of ST-segment deviation in leads II, III and aVF, such that a lower score was accompanied by more inferior ST depression, and a higher one by inferior ST-segment elevation (Figure 3). Similar results ($r = 0.52$) were obtained when the contribution to the angiographic score of vessels proximal to the occlusion was decreased by 50%.

Each element of the angiographic score was analyzed separately. Inferior ST-segment depression was significantly less in patients ($n = 33$) whose LAD coronary artery extended around the apex to supply part of the inferior wall compared with that of those ($n = 9$) in whom the vessel terminated at or before the cardiac apex (0.2 ± 4.0 vs -3.0 ± 2.8 mm; $p < 0.05$). There was a significant correlation ($r = 0.59$; $p < 0.01$) between the number of branch vessels proximal to the site of the LAD coronary artery occlusion and the net inferior ST-segment deviation (Figure 4). There were only 5 patients with collateral flow from the LAD coronary artery to the inferior wall of the left ventricle. Although the mean inferior ST-segment depression was less in these patients than in the 37 without such collateral flow (-0.2 ± 6.7 vs -0.6 ± 3.7 mm), this difference was not statistically significant. All results were similar when patients with history of AMI were excluded from the analysis.

Because the number of patent vessels proximal to the site of the LAD artery occlusion appeared to be a powerful predictor of inferior ST-segment deviation, multiple regression analysis was performed to determine if the anatomic extent of the LAD artery had an independent influence on the inferior ST segment. In this analysis, the independent effect of a wrap around LAD artery was of borderline statistical significance ($p = 0.07$) when the site of occlusion was taken into account.

Creatine phosphokinase-MB isoenzyme levels: In the 38 patients with ≥1 value above the normal range (no measurement was obtained in 1 patient), a greater number of perfused LAD artery branches proximal to the occlusion was associated with lower peak creatine phosphokinase-MB isoenzyme levels ($r = -0.39$; $p < 0.05$) (Figure 5).

There were 9 patients whose LAD coronary artery did not wrap around the cardiac apex. In this group, one would expect only the anterior wall, and not a portion of the inferior wall, to have ischemia and AMI. These pa-

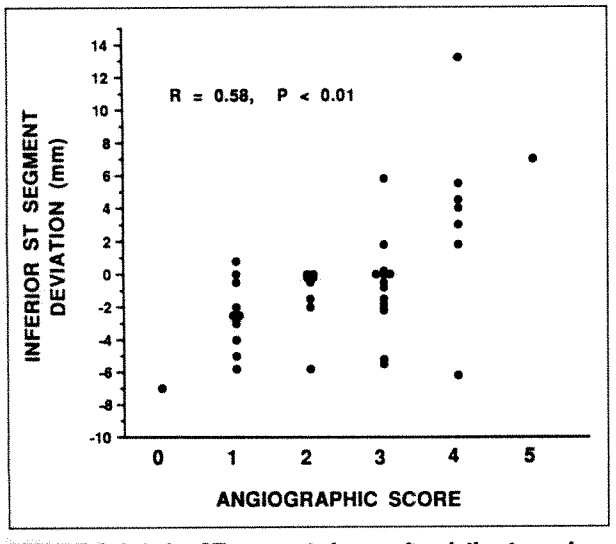


FIGURE 3. Inferior ST-segment changes in relation to angiographic score in each patient. *Ordinate* indicates sum of ST-segment deviation in leads II, III and aVF, with positive values representing net ST-segment elevation, and negative values net ST-segment depression. Relation persists ($r = 0.52$, $p < 0.001$) even when 2 highest and lowest values are excluded or when each patent proximal vessel contributes ½ point (rather than 1) to angiographic score ($r = 0.52$).

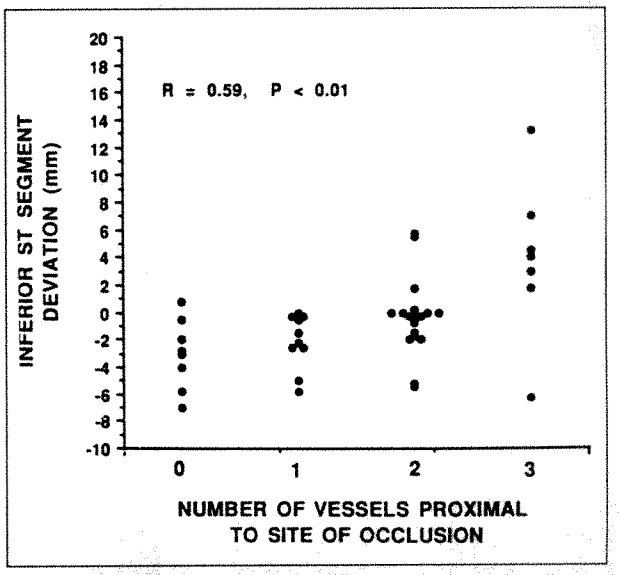


FIGURE 4. Inferior ST-segment changes in each patient in relation to location of the left anterior descending artery occlusion. *Ordinate* is as in Figure 2. *Abscissa* indicates number of major branch vessels (see text) proximal to occlusion.

tients displayed a significant positive correlation between creatine phosphokinase-MB levels and the magnitude of inferior ST-segment depression ($r = 0.69$; $p < 0.05$) (Figure 6).

DISCUSSION

Prior studies relating to inferior ST-segment elevation in anterior myocardial infarction: Studies of the occurrence and clinical significance of reciprocal ST-segment depression in AMI have supported 2 concepts.[2] First, reciprocal ST-segment depression is often associated with more ischemic or damaged myocardium in the infarct region, and thus represents a purely electrical phenomenon determined by the presence and magnitude of the injury current dipole. Second, many patients with reciprocal ST-segment depression have critical coronary artery stenoses and segmental dysfunction in myocardial regions remote from that of the AMI, suggesting that "ischemia at a distance" is also an important contributor to reciprocal ST-segment depression. Subendocardial rather than transmural ischemia is assumed to exist in the remote zone, because the former would be expected to produce ST-segment depression.[8]

In contrast, transmural myocardial ischemia could coexist in both the primary infarct zone and remote areas. In the case of anterior AMI, concomitant inferior transmural ischemia should cause the inferior ST segments to shift upward rather than downward. It was previously shown that patients with an anterior AMI and wrap around LAD coronary artery have less inferior ST-segment depression,[3] and a few apparently had inferior ST-segment elevation. There is little additional information concerning the anterior–inferior AMI electrocardiographic pattern. One recent case report described a patient with simultaneous acute anterior and inferior ST-segment elevations who had occlusion of an LAD coronary artery that supplied one third of the inferior wall.[4] Another study described several patients with 1-vessel disease involving a wrap around LAD artery who displayed both anterior and inferior Q waves.[5] Finally, an older autopsy study reported that when anterior AMI was accompanied by a histologically simultaneous "posterior" AMI, the reciprocal ST-segment depression "commonly" seen in lead aVF was not found in any of 19 cases.[6]

Further insight into the "anterior–inferior" infarction electrocardiogram: Pathoanatomic reports suggest that most patients have a wrap around LAD coronary artery,[9] and in our study, 33 of 42 patients had this anatomy. Our study attempts to explain why only 7 of the 33 patients demonstrated the anterior–inferior AMI electrocardiographic pattern. Patients with an LAD coronary artery that was occluded proximally and did not extend to the inferior wall had the most inferior ST-segment depression. Presumably these patients had a larger mass of ischemic anterior wall myocardium and were least likely to have inferior wall transmural ischemia. The 7 patients with the anterior–inferior AMI electrocardiographic pattern were distinguished by the distal location of the LAD coronary artery occlusion (beyond 2 major branches in 2 patients, and beyond 3 branches in the other 5). We postulate that the inferior wall injury current must be combined with the weak reciprocal of a smaller anterior injury current to generate the unusual acute anterior–inferior AMI pattern on the 12-lead electrocardiogram.

An important angiographic feature of the LAD artery related to the magnitude and direction of inferior ST-segment deviation was the number of branches proximal to the occlusion. That this feature is related to infarct size is supported by observations in an animal model,[10] postmortem human hearts[11] and patients with AMI.[3] The relation of infarct size to the magnitude of the anteriorly directed injury current and its reciprocal is also seen in experimental data[12] and clinical stud-

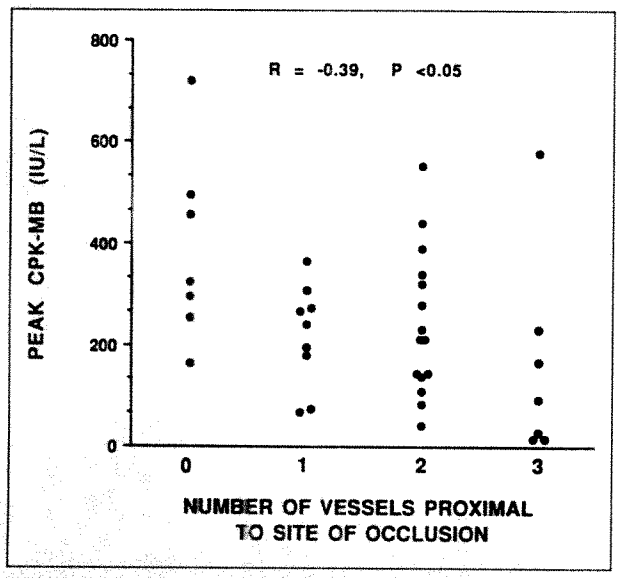


FIGURE 5. Peak creatine phosphokinase (CPK)-MB level for each patient with abnormal elevation after prolonged chest pain in relation to location of left anterior descending artery occlusion (*abscissa* as in Figure 4).

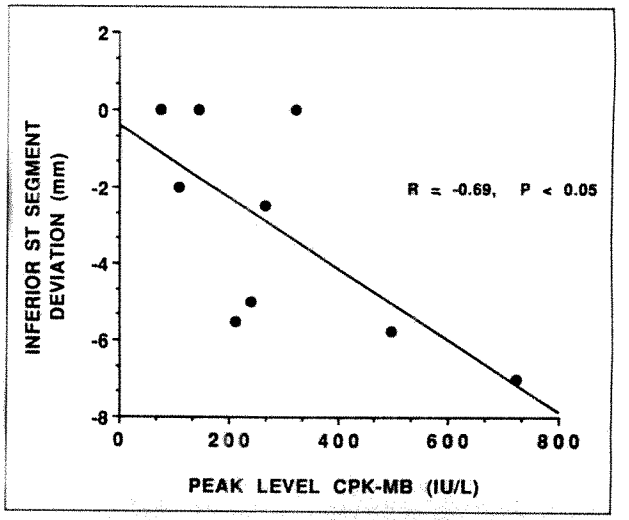


FIGURE 6. Relation between reciprocal inferior ST-segment changes (*ordinate* as in Figure 2) and peak creatine phosphokinase (CPK)-MB (*abscissa* as in Figure 5) in patients with left anterior descending artery that did not extend beyond cardiac apex.

ies.[13–20] Simultaneous anterior and inferior ST-segment elevation can also be seen in the setting of right coronary artery occlusion.[21] However, in this case, leads V_1 and V_2 have greater ST-segment elevation than do V_3 and V_4, a pattern not seen in any patient in this study.

Study limitations: Several methodologic considerations could have affected the results of this study. First, angiographic recognition of the lesion responsible for AMI can be difficult when angiography is performed several days after AMI. In some patients there can be a rapid, marked decrease in the degree of coronary narrowing after occlusion and reperfusion, leaving a residual stenosis of <50%.[7] Second, the use of angiography to estimate the volume of myocardium affected by a coronary artery occlusion is not precise, and the use of cardiac isoenzyme levels to estimate infarct size is hampered by variations in sampling times and therapeutic interventions such as thrombolytic agents, percutaneous transluminal coronary angioplasty and other medical therapies. Other methods of assessing infarct size may have yielded a better correlation between infarct size and reciprocal ST-segment depression. Third, we did not confirm the presence of inferior wall ischemia in patients with a wrap around LAD artery. However, an earlier study did show similar coronary anatomy to be associated with an inferior wall thallium defect in 13 of 15 patients.[3] Finally, this study does not take into account other factors known to influence the magnitude of ST-segment deviation during coronary occlusion. These factors include infarct shape and boundary location, presence of subendocardial as opposed to transmural myocardial ischemia, prior tissue infarction, local metabolic factors and time course of cellular electrical uncoupling.[8,22] However, there is no reason to assume that any of these methodologic considerations biased the results of the study.

Clinical implications: In some situations therapy may be influenced by the identification of a lesion in the proximal versus the distal LAD coronary artery. Studies of patients with stable coronary disease have suggested that proximal LAD coronary artery disease may cause greater ventricular dysfunction during exercise,[23] a lower ejection fraction after AMI,[24–25] and a more adverse long-term prognosis[25–26] than may distal disease. Our study shows that despite the electrocardiographic appearance of more widespread ischemia patients with the anterior–inferior AMI pattern frequently had relatively distal LAD artery lesions. Although the mean ejection fraction in the 7 patients with this electrocardiographic pattern was greater than that of the other 35 (0.55 vs 0.48) and the 16 with the most proximal lesions (0.42), the differences were not significant. Because our sample size is relatively small, further study is warranted to determine if this electrocardiographic pattern identifies a clinically distinct subset with improved left ventricular function after AMI.

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Influence of Thrombolysis on Signal-Averaged Electrocardiogram and Late Arrhythmic Events After Acute Myocardial Infarction

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The influence of intravenous thrombolysis on both prevalence of ventricular late potentials and incidence of late arrhythmic events was evaluated in 174 consecutive patients surviving a first acute myocardial infarction; 106 patients (61%) received thrombolysis (group A) and 68 (34%) had conventional therapy (group B). In group A, 18 patients (17%) had late potentials compared with 23 (34%) in group B ($p < 0.05$); mean left ventricular ejection fraction was not different (0.50 ± 0.09 vs 0.50 ± 0.10; p = not significant [NS]). Of 63 patients who underwent coronary arteriography because of postinfarction ischemia, 28 (44%) had a closed infarct-related artery; of these, 11 (39%) had late potentials compared with 3 of 35 (9%) with a patent artery ($p < 0.01$). Mean left ventricular ejection fraction was not significantly different between the 2 groups (0.49 ± 0.09 vs 0.53 ± 0.09; p = NS). At a mean follow-up of 14 ± 8 months, 8 of 161 patients (5%) had a late arrhythmic event; 6 of 8 (75%) with and 28 of 153 (18%) without events had late potentials ($p < 0.001$). In group A, 4 of 99 patients (4%) had events compared with 4 of 62 (6%) in group B (p = NS, relative risk 1.6). Of 24 patients with anterior wall AMI and left ventricular dyskinesia, 6 events occurred. In this group of patients, a higher rate of events was observed (25%); 3 of 16 (19%) treated with thrombolysis had an event compared with 3 of 8 (37%) treated conventionally (p = NS, relative risk 2.6). Thrombolysis and patency of the infarct-related artery significantly reduce the rate of late potentials independently of global left ventricular function. Although no significant difference was found in the follow-up results, the reduced rate of late potentials suggests an improved ventricular electrical stability both in patients treated with thrombolysis and in those with a patent vessel.

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The early fibrinolytic treatment of acute myocardial infarction (AMI) improves survival by reducing infarct size and left ventricular dysfunction.[1] However, thrombolytic therapy decreases mortality also in the absence of demonstrable myocardial salvage, and patency of the infarct-related coronary artery appears to be an important independent predictor of survival.[1] Therefore, the reduction of left ventricular impairment is not the only mechanism responsible for improved survival in patients treated with thrombolysis; both limitation of remodeling of the left ventricle and increased electrical heart stability could have an important role.[1] The signal-averaged electrocardiogram (SAECG) allows the noninvasive detection of late potentials at the end of or after the QRS complex.[2] Late potentials represent low-amplitude fractionated electrical activity, are markers for an "arrhythmogenic substrate" that may become the site for re-entry,[3] and provide important prognostic information in identifying patients at risk of arrhythmic events after AMI.[4–8] Controversial data are available concerning the influence of fibrinolytic treatment on the prevalence of ventricular late potentials,[9–15] and the effect of both thrombolysis and coronary reperfusion on late arrhythmic events after AMI is unknown. Furthermore, no data are available concerning a possible influence of thrombolysis on the predictive ability of the SAECG for post-AMI arrhythmic events.[16] We performed a prospective study of unselected patients surviving a first AMI to assess: (1) the influence of intravenous thrombolysis on both the rate of late potentials and ventricular ectopic activity, (2) the influence of patency of the infarct-related coronary artery on the SAECG, (3) the possible influence of intravenous thrombolysis on late potentials as markers of future malignant ventricular tachyarrhythmias, (4) and the possible influence of fibrinolysis on the occurrence of late arrhythmic events after AMI.

METHODS

Patient population: From May 1989 to December 1990, 174 consecutive patients surviving a first AMI, and admitted to our institute for functional evaluation and cardiac rehabilitation were enrolled in the present study. Of patients included in the study, 106 (61%) received intravenous thrombolytic therapy within 6 hours of the onset of symptoms, and 68 (39%) were treated conventionally because of late hospitalization or contraindications to fibrinolytic treatment. In the group treated with thrombolysis, 58 patients (55%) received streptokinase (1.5 million U over 30 to 60 minutes), 17

(16%) received urokinase (1.5 to 2 million U over 60 minutes), and 31 (29%) received recombinant tissue-type plasminogen activator (100 mg over 180 minutes). All patients aged >70 years with bundle branch block, flutter or atrial fibrillation (or both), ventricular paced rhythm, heart failure, unstable angina, balloon angioplasty or coronary artery grafting before being admitted to our institute, or on amiodarone treatment, and with poor quality echocardiograms were excluded from the study. Patients (159 men and 15 women) had a mean age of 54 ± 8 years. AMI was anterior in 76 patients (44%), inferior in 98 (56%), and non-Q-wave in 43 (25%). Ventricular fibrillation during the first 5 days after AMI occurred in 21 patients (12%).

Study design: A maximal exercise test, Holter monitoring and an SAECG were performed with pharmacologic wash-out in all except 5 patients. In 3 and 2 cases exercise testing and Holter monitoring, respectively, were performed with pharmacologic treatment, owing to technical problems. These 5 tests were excluded from the analysis of the results. The period of washout from digitalis, β blockers, calcium antagonists and antiarrhythmic drugs was ≥5 times the half-life of the drug. In all patients, 2-dimensional echocardiography was performed on admission to our institute. Antiarrhythmic agents were administered to 6 patients after the occurrence of a late sustained ventricular arrhythmia. Antiarrhythmic drugs were administered to 12 subjects who were asymptomatic for late sustained ventricular arrhythmias. These patients (considered at high risk of late arrhythmic events after the noninvasive evaluation owing to the presence of ≥2 of the following criteria: left ventricular ejection fraction <0.40, ventricular late potentials, and Lown 4A–B class ventricular ectopic beats) received antiarrhythmic therapy, because sustained monomorphic ventricular tachycardia was inducible by programmed electrical stimulation. They were excluded from the analysis of the follow-up results, because drug therapy may modify the spontaneous occurrence of late arrhythmic events. The use of β-adrenergic blocking agents was not standardized and was left to the discretion of the attending physician.

Follow-up data of 162 patients were analyzed; 82 (51%) were recalled for assessment of clinical status, and 80 (49%) had follow-up contact by phone. A "late arrhythmic event" was defined as sudden death or the occurrence of symptomatic or sustained ventricular arrhythmia 5 days after AMI. Sudden death was defined as a witnessed, unexpected death occurring within 1 hour of the onset of symptoms. Sustained ventricular arrhythmia was defined as spontaneous ventricular fibrillation or tachycardia lasting >30 seconds or necessitating cardioversion because of hemodynamic collapse.

Signal-averaged electrocardiogram: An SAECG was obtained in all patients 26 ± 10 days (range 8 to 49) after AMI using a commercial Fidelity Medical LP 3000 system. With standard bipolar orthogonal X, Y and Z leads, signals from 175 ± 55 beats were amplified, digitized, averaged and then filtered (band-pass filter range 40 to 250 Hz) with a Butterworth bidirectional filter. The signals from each of the 3 leads were combined into a vector magnitude composite electrogram obtained by taking the square root of the sum of the squares of the readings from the individual leads. A computerized algorithm determined the onset and offset of the QRS complex and calculated the filtered QRS duration, the duration of the terminal low-amplitude QRS signals (<40 μV), and the root-mean-square voltage of the last 40 ms of the filtered QRS complex. Measurement of the duration of the QRS complex was confirmed visually in each case by 2 investigators. Recordings with a noise level >0.5 μV were rejected. The mean noise level in the late ST segment was 0.36 ± 0.16 μV. Recently, for a band-pass filter range of 40 to 250 Hz, the normal values of an SAECG were defined as follows: filtered QRS duration ≤114 ms, root-mean-square voltage ≥20 μV, and terminal low-amplitude signal duration ≤38 ms.[17] We confirmed similar normal values using the Fidelity Medical LP 3000 system. We recorded the SAECG with a band-pass filter range of 40 to 250 Hz in a group of 24 normal subjects (mean age 26 ± 5 years; group I); mean filtered QRS duration was 96 ± 11 ms, root-mean-square voltage was 57 ± 40 μV, and terminal low-amplitude signal duration was 30 ± 5 ms. Measurements from group I were used to calculate the 95% confidence limits of normal subjects, considering SAECG determinants to be in a Gaussian distribution. Normal values of duration of both filtered QRS (≤114 ms) and terminal low-amplitude signals (≤38 μV) were defined as mean ± 1.645 standard deviation. The root-mean-square voltage was between 17 and 20 μV in 4 normal subjects (17%). Of 21 patients (mean age 53 ± 9 years; group II) randomly selected from a group of 180 consecutive patients with previous AMI and absence of late sustained or nonsustained ventricular tachycardia, root-mean-square voltage was <20 μV in 5 (24%) and <17 μV in 4 (19%). Of 13 consecutive patients (mean age 57 ± 9 years; group III) who developed late sustained ventricular tachycardia or fibrillation, or both, root-mean-square voltage was <20 μV in 9 (69%) and <17 μV in 7 (54%). Even if >5% of normal subjects had root-mean-square voltage <20 μV, a value of <20 μV was considered abnormal for both the sake of uniformity and comparative purposes, because most laboratories use this value for defining an abnormal value when assessing this variable at 40 Hz. Furthermore, 2 of 13 patients (15%) with a late sustained ventricular arrhythmia had root-mean-square voltage between 17 and 20 μV. At least 2 SAECG determinants were abnormal in 9 of 13 patients (69%) in group III, in 4 of 21 (19%) in group II, and in no subject in group I. Therefore, late potentials were considered present if ≥2 SAECG determinants were abnormal. In 110 of 174 patients (63%) also, an SAECG with a band-pass filter range of 25 to 250 Hz was available. According to the criteria of Simson,[2] using 25 Hz high-pass filtering, the normal values of the SAECG were defined as follows: filtered QRS duration ≤120 ms, and root-mean-square voltage ≥25 μV. The abnormality of ≥1 of these criteria defined the test as pathologic.

Holter monitoring: Holter monitoring (recorded 23 ± 9 days after AMI with pharmacologic washout) was available in 172 patients: 112 (65%) underwent 48-hour Holter monitoring, and 60 (35%) had 24-hour monitor-

TABLE I Characteristics of Patients With and Without Thrombolysis for Acute Myocardial Infarction

	Thrombolysis (n = 106)	No Thrombolysis (n = 68)	p Value
Clinical data			
Age (yr)	53 ± 9	55 ± 8	NS
Men/women	100/6	59/9	NS
VF 0–5 days after AMI	14/106 (13)	7/68 (10)	NS
Anterior AMI (%)	44/106 (41)	32/68 (47)	NS
Inferior AMI (%)	62/106 (59)	36/68 (53)	NS
Non-Q-wave AMI (%)	20/106 (19)	23/68 (34)	<0.05
2-dimensional echocardiographic data			
LVEF	0.50 ± 0.09	0.50 ± 0.10	NS
Dyskinesia (%)	21/106 (20)	14/68 (21)	NS
Signal-averaged ECG data			
LP(%)	18/106 (17)	23/68 (34)	<0.05
QRSD (ms)	99 ± 10	103 ± 11	<0.05
RMS40 (μV)	48 ± 35	37 ± 32	<0.05
LAS40 (ms)	31 ± 14	34 ± 11	NS
Holter monitoring data			
VPCs/hours (n)	7 ± 25	10 ± 24	NS
Lown 1–3 VPCs (%)	52/105 (50)	36/67 (54)	NS
Lown 4A VPCs (%)	18/105 (17)	14/67 (21)	NS
Lown 4B VPCs (%)	32/105 (30)	16/67 (24)	NS
Exercise test data			
No VPCs (%)	68/106 (64)	39/65 (60)	NS
Lown 1–3 VPCs (%)	32/106 (30)	19/65 (29)	NS
Lown ≥ 4 VPCs (%)	6/106 (6)	7/65 (11)	NS

Continuous variables are expressed as mean ± 1 SD.
AMI = acute myocardial infarction; ECG = electrocardiographic; LAS40 = duration of low-amplitude signals <40 μV; LP = late potentials; LVEF = left ventricular ejection fraction; NS = not significant; QRSD = duration of filtered QRS complex; RMS40 = root-mean-square voltage of last 40 ms of filtered QRS complex; VF = ventricular fibrillation; VPCs = ventricular premature complexes.

TABLE II Characteristics of Patients With and Without Late Potentials

	Late Potentials (n = 41)	No Late Potentials (n = 133)	p Value
Clinical data			
Age (yr)	56 ± 8	53 ± 8	<0.05
Men/women	36/5	123/10	NS
VF 0–5 days after AMI	8/41 (19)	13/133 (10)	NS
Anterior AMI (%)	16/41 (39)	60/133 (45)	NS
Inferior AMI (%)	25/41 (61)	73/133 (55)	NS
Non-Q-wave AMI (%)	9/41 (22)	34/133 (26)	NS
2-dimensional echocardiographic data			
LVEF	0.45 ± 0.11	0.51 ± 0.08	<0.001
Dyskinesia (%)	12/41 (29)	23/133 (17)	NS
Holter monitoring data			
VPCs/hours (n)	8 ± 22	8 ± 26	NS
Lown 1–3 VPCs (%)	23/39 (59)	64/133 (48)	NS
Lown 4A VPCs (%)	8/39 (21)	24/133 (18)	NS
Lown 4B VPCs (%)	8/39 (21)	40/133 (30)	NS
Exercise test data			
No VPCs (%)	24/38 (63)	83/133 (62)	NS
Lown 1–3 VPCs (%)	12/38 (32)	39/133 (29)	NS
Lown ≥ 4 VPCs (%)	2/38 (5)	11/133 (8)	NS

Abbreviations as in Table I.

ing. A 3-channel electrocardiogram (ECG) was analyzed with a Marquette Electronics Holter 8000 T analysis system; 4 investigators verified the detection and interpretation of ventricular arrhythmias. Lown class and the number of premature ventricular complexes were assessed.

Other diagnostic procedures: In all patients, a 2-dimensional echocardiogram using a Ving Med CFM 750 unit was obtained 21 ± 10 days after AMI. Evaluation of left ventricular ejection fraction by Simpson's formula, and detection of left ventricular dyskinesia were performed. With pharmacologic washout, a maximal exercise test according to Bruce's protocol was performed by 171 patients on a Marquette Electronics Case 12 treadmill 27 ± 10 days after AMI, and the Lown class of ventricular ectopic beats was evaluated. Owing to post-AMI myocardial ischemia, coronary arteriography was performed in 63 patients (36%) 43 ± 22 days after AMI. Cardiac catheterization was performed by angiographers who were not investigators in this study. The artery involved in the AMI was identified on the basis of the location of the AMI as determined by electrocardiography. The infarct-related artery was considered open in the case of partial or complete anterograde perfusion. The complete absence of anterograde perfusion defined the artery as occluded.

Statistical analysis: Continuous variables were compared using Student's unpaired *t* test, and proportional differences were compared by chi-square analysis with Yates' correction for continuity. Continuous variables were expressed as mean ± 1 standard deviation. Logistic regression analysis was performed with late potentials as the dependent variable, and age, AMI location, development of pathologic Q waves, left ventricular ejection fraction, and dyskinesia, thrombolytic therapy and status (patent or closed) of infarct-related artery as independent variables. A p value <0.05 was considered statistically significant. The standard definitions for sensitivity, specificity, and positive and negative predictive values were used.

RESULTS

Comparison of patients with and without thrombolytic therapy: Prevalence of both non-Q-wave AMI and ventricular late potentials was significantly different between the 2 groups of patients. Prevalence of non-Q-wave AMI was significantly (p <0.05) lower in the group treated with thrombolysis, as well as rate of late potentials (p <0.05), using a band-pass filter range of 40 to 250 Hz (Table I). In the group treated with thrombolysis, filtered QRS duration was significantly (p <0.05) lower, and terminal root-mean-square voltage was significantly (p <0.05) higher than in the control group; no significant difference was observed regarding duration of terminal low-amplitude signals (Table I). Of 58 patients treated with streptokinase, 10 (17%) had late potentials compared with 4 of 31 (13%) treated with recombinant-tissue plasminogen activator, and 4 of 17 (23%) treated with urokinase (p = not significant [NS]).

In 110 patients, an SAECG with both band-pass filter ranges of 40 to 250 and 25 to 250 Hz was available. We compared 75 patients (68%) treated with throm-

TABLE III Characteristics of Patients With and Without a Patent Infarct-Related Artery

	Patency of the Infarct-Related Artery (n = 35)	Occlusion of the Infarct-Related Artery (n = 28)	p Value
Clinical data			
Age (yr)	49 ± 8	52 ± 8	NS
Men/women	32/3	27/1	NS
VF 0–5 days after AMI	5/35 (14)	3/28 (11)	NS
Anterior AMI (%)	18/35 (51)	13/28 (46)	NS
Inferior AMI (%)	17/35 (49)	15/28 (54)	NS
Non-Q-wave AMI (%)	14/35 (40)	7/28 (25)	NS
Thrombolysis (%)	23/35 (66)	10/28 (36)	<0.05
No thrombolysis (%)	12/35 (34)	18/28 (64)	<0.05
2-dimensional echocardiographic data			
LVEF	0.53 ± 0.09	0.49 ± 0.09	NS
Dyskinesia (%)	6/35 (17)	7/28 (25)	NS
Signal-averaged ECG data			
LP (%)	3/35 (9)	11/28 (39)	<0.01
QRSD (ms)	97 ± 7	105 ± 11	<0.01
RMS40 (μV)	52 ± 29	31 ± 35	<0.05
LAS40 (ms)	27 ± 6	36 ± 12	<0.001
Holter monitoring data			
VPCs/hours (n)	4 ± 14	7 ± 19	NS
Lown 1–3 VPCs (%)	15/35 (43)	15/28 (54)	NS
Lown 4A VPCs (%)	9/35 (26)	2/28 (7)	NS
Lown 4B VPCs (%)	11/35 (31)	11/28 (39)	NS
Exercise test data			
No VPCs (%)	27/35 (77)	16/27 (59)	NS
Lown 1–3 VPCs (%)	6/35 (17)	10/27 (37)	NS
Lown ≥4 VPCs (%)	2/35 (6)	1/27 (4)	NS

Abbreviations as in Table I.

TABLE IV Characteristics of Patients With and Without Late Arrhythmic Events

	Arrhythmic Events (n = 8)	No Arrhythmic Events (n = 153)	p Value
Clinical data			
Age (yr)	53 ± 9	54 ± 8	NS
Men/women	8/0	139/14	NS
VF 0–5 days after AMI	1/8 (12)	18/153 (12)	NS
Anterior AMI (%)	7/8 (88)	62/153 (40)	<0.05
Inferior AMI (%)	1/8 (12)	91/153 (60)	<0.05
Non-Q-wave AMI (%)	1/8 (12)	40/153 (26)	NS
Thrombolysis (%)	4/8 (50)	95/153 (62)	NS
No thrombolysis (%)	4/8 (50)	58/153 (38)	NS
2-dimensional echocardiographic data			
LVEF	0.35 ± 0.06	0.51 ± 0.08	<0.001
Dyskinesia (%)	6/8 (75)	25/153 (16)	<0.001
Signal-averaged ECG data			
LP(%)	6/8 (75)	28/153 (18)	<0.001
QRSD (ms)	111 ± 10	99 ± 10	<0.01
RMS40 (μV)	18 ± 16	46 ± 35	<0.05
LAS40 (ms)	42 ± 13	31 ± 13	<0.05
Holter monitoring data			
VPCs/hours (n)	16 ± 32	8 ± 25	NS
Lown 1–3 VPCs (%)	1/6 (17)	87/153 (57)	NS
Lown 4A VPCs (%)	0/6 (0)	31/153 (20)	NS
Lown 4B VPCs (%)	5/6 (83)	35/153 (23)	<0.01
Exercise test data			
No VPCs (%)	3/6 (50)	95/152 (62)	NS
Lown 1–3 VPCs (%)	3/6 (50)	45/152 (30)	NS
Lown ≥4 VPCs (%)	0/6 (0)	12/152 (8)	NS

Abbreviations as in Table I.

bolysis with 35 (32%) treated conventionally. With a band-pass filter range of 40 to 250 Hz, we observed significant differences in filtered QRS duration (98 ± 10 vs 105 ± 11 ms; $p < 0.01$), terminal root-mean-square voltage (53 ± 36 vs 32 ± 25 μV; $p < 0.01$) and duration of terminal low-amplitude QRS signals (29 ± 9 vs 36 ± 12 ms; $p < 0.01$). The rate of late potentials was significantly lower in the group treated with thrombolysis (10 of 75 [13%] vs 15 of 35 [43%]; $p < 0.01$). With a band-pass filter range of 25 to 250 Hz, no significant difference was observed regarding filtered QRS duration (105 ± 10 vs 104 ± 14 ms; p = NS), terminal root-mean-square voltage (64 ± 47 vs 71 ± 48 μV; p = NS), duration of terminal low-amplitude QRS signals (28 ± 12 vs 26 ± 9 ms; p = NS) and prevalence of SAECG abnormalities (17 of 75 [23%] vs 9 of 35 [26%]; p = NS).

Comparison of patients with and without ventricular late potentials: Among the variables considered, only age and left ventricular ejection fraction were significantly different between the 2 groups of patients: mean age was significantly ($p < 0.05$) higher and mean ejection fraction significantly ($p < 0.001$) lower in the group with late potentials (Table II).

Comparison of patients with and without patency of the infarct-related coronary artery: Of patients with a closed infarct-related artery, the prevalence of late potentials was significantly ($p < 0.01$) higher than in the group with a patent vessel (Table III); also, filtered QRS duration ($p < 0.01$), duration of terminal low-amplitude signals ($p < 0.001$), and terminal root-mean-square voltage ($p < 0.05$) were significantly different (Table III). Late potentials had sensitivity and specificity for a closed infarct-related coronary artery of 39 and 91%, respectively. The positive and negative predictive values were 79 and 65%, respectively. No other comparisons were statistically significant, except for the thrombolytic therapy rate in the group with a patent artery; a significantly ($p < 0.05$) higher number of patients than that in the group with a closed vessel received thrombolysis (Table III).

Of 63 patients who underwent coronary arteriography, 30 (48%) did not receive thrombolysis; 12 (40%) of these had patency of the infarct-related artery, whereas 18 (60%) had a closed vessel. In the group with a patent artery, 1 of 12 patients (8%) had late potentials compared with 7 of 18 (39%) with a closed artery (p = NS). We compared mean values of filtered QRS duration (101 ± 8 vs 103 ± 10 ms; p = NS) and terminal root-mean-square voltage (48 ± 24 vs 35 ± 41 μV; p = NS); no significant difference was found between the 2 groups. Conversely, duration of terminal low-amplitude QRS signals (26 ± 8 vs 35 ± 10 ms; $p < 0.05$) was significantly lower in the group with a patent vessel. Mean left ventricular ejection fraction was not significantly different (0.51 ± 0.10 vs 0.54 ± 0.09; p = NS).

Follow-up data: At a mean follow-up of 14 ± 8 months after AMI, 8 of 161 patients (5%) developed a late arrhythmic event; 6 of 8 events (75%) occurred in the first 2 months after AMI (mean 21 ± 18 days, range 6 to 55). Conversely, only 2 events (25%) were observed 11 and 16 months after AMI. Sudden death occurred in 2 patients, 4 had sustained ventricular tachycardia, and 2 had aborted sudden death with evidence of ventricular fibrillation at the time of cardioversion. Syncope and cardiac arrest with recovery of spontaneous cardiac activity after a short cardiopulmonary reanimation were observed in 1 patient. In this patient, heart rhythm during the cardiac arrest was not documented, and the electrophysiologic study was not performed, because the patient did not consent. Therefore, this event was not included in the statistical analysis. None of 6 patients with late sustained ventricular tachyarrhythmias developed new Q waves on ECG.

Anterior site of AMI ($p < 0.05$), left ventricular dyskinesia ($p < 0.001$) and ejection fraction ($p < 0.001$), late potentials ($p < 0.001$), filtered QRS duration ($p < 0.01$), terminal root-mean-square voltage ($p < 0.05$), duration of terminal low-amplitude signals ($p < 0.05$), and Lown 4B-class ventricular ectopic beats on Holter monitoring ($p < 0.01$) had a significant relation to late arrhythmic events (Table IV).

In the general population of the study, sensitivity, specificity, and positive and negative predictive values of late potentials for late arrhythmic events were 75, 82, 18 and 98%, respectively. Of 99 patients treated with thrombolysis, the significant relation between late potentials and arrhythmic events was preserved. Arrhythmic events occurred in 4 of 99 patients (4%) treated with thrombolysis; 3 (75%) of these had late potentials compared with 13 of 95 (14%) without events ($p < 0.05$). In the group treated with thrombolysis, sensitivity, specificity, and positive and negative predictive values of late potentials for late arrhythmic events were 75, 86, 19 and 99%, respectively.

Regarding the prevalence of thrombolytic therapy, no significant difference was found between the 2 groups of patients with and without events (Table IV). Patients with conventional therapy had a relative risk of developing late arrhythmic events of 1.6 compared with those treated with thrombolysis. Of patients with late arrhythmic events, 6 of 8 (75%) had both anterior wall AMI and left ventricular dyskinesia; thus, in this group the event rate was 25% (6 of 24). Regarding fibrinolytic treatment, 16 of 24 patients (67%) received thrombolysis, and 8 (33%) were treated conventionally. In the group treated with thrombolysis, 3 of 16 patients (19%) developed late arrhythmic events compared with 3 of 8 (37%) in the control group ($p = NS$). Mean left ventricular ejection fraction was not significantly different (0.38 ± 0.09 vs 0.38 ± 0.06; $p = NS$). Of patients with anterior wall AMI and left ventricular dyskinesia, the relative risk of developing late arrhythmic events was 2.6 without thrombolytic therapy.

Multivariate analysis: We performed a stepwise logistic regression analysis to assess the relation between late potentials and independent variables such as age, AMI location, development of pathologic Q waves, left ventricular ejection fraction and dyskinesia, and thrombolytic therapy. Left ventricular ejection fraction ($p < 0.001$), AMI location ($p < 0.01$) and thrombolytic therapy ($p < 0.01$) were found to be independent predictors of late potentials. We performed a similar analysis in the group of 63 patients who underwent coronary arteriography, including the status of the infarct-related coronary artery among independent variables. The status of the infarct-related artery was found to be the only independent predictor of late potentials ($p < 0.01$); left ventricular ejection fraction and thrombolytic therapy did not reach levels of significance.

DISCUSSION

This study, in agreement with other reports,[9,10,12,13,15] found a significantly lower prevalence of late potentials in the group treated with thrombolysis. Regarding the rate of late potentials and the SAECG quantitative analysis, a significant difference between the 2 groups of patients with and without thrombolysis was observed only using a band-pass filter range of 40 to 250 Hz; no difference was present using 25 Hz high-pass filtering. This result is in agreement with the data of Chew et al.[13] Therefore, a band-pass filter range of 25 to 250 Hz could undervalue the presence of late potentials, as found by Gomes et al[18] and Denes et al.[19] Therefore, in the study of Turitto et al[11] the absence of a significant difference in the prevalence of late potentials between patients treated with thrombolysis and control subjects could be related to the use of 25 Hz high-pass filtering.

According to other investigators,[8,20,21] the presence of late potentials seemed to characterize patients with greater left ventricular dysfunction. Greater infarct size and left ventricular dysfunction are associated with late potentials. Therefore, early reperfusion and reduction of the left ventricular impairment could prevent SAECG abnormalities. In our study, as in others,[9,13–15,22] a significant correlation between patency of the infarct-related coronary artery and reduced prevalence of late potentials was found, and the multivariate analysis showed the status (patency or occlusion) of the infarct-related artery to be the only independent predictor of late potentials. Therefore, occlusion of the infarct-related coronary artery appears to be the most important cause of late potentials, independent of global left ventricular function. Late potentials were specific markers of occlusion of the infarct-related coronary artery; this finding could have great clinical relevance, because patency of the infarct-related artery represents an independent predictor of survival.[1] However, in the present study, cardiac catheterization was performed because of post-AMI ischemia, and this fact may represent a possible selection bias; even the small number of patients who underwent coronary arteriography represents a limitation of our study.

No data are available concerning the influence of late reperfusion on the prevalence of late potentials. Vatterott et al[14] found that a patent vessel was not associated with a statistically significant reduction in the

rate of late potentials without reperfusion therapy in the acute stage of AMI. Nevertheless, of patients not undergoing early therapy directed toward achieving reperfusion, a significantly lower filtered QRS duration was observed when the infarct-related artery was patent. In our study, coronary arteriography was available in 30 patients not treated with thrombolysis. In this group, spontaneous reperfusion may have been a late phenomenon beyond the conventionally accepted period during which reperfusion can modify infarct size. Quantitative analysis of the SAECG showed that the duration of terminal low-amplitude signals was significantly lower in the group with a patent vessel. The number of patients studied (48 in the study of Vatterott et al,[14] and 30 in our study) is too small to advance conclusions, but a beneficial effect of late reperfusion on the development of late potentials can be hypothesized, because statistical analysis showed a favourable effect of patency of the infarct-related coronary artery on 2 determinants of the SAECG (filtered QRS duration in Vatterott's study,[14] and duration of terminal low-amplitude signals in our study). The results of a recent study by Lacroix et al[21] were in compliance with this possibility; in fact, in a group of patients with coronary artery disease, they documented a reduction of 65% in the prevalence of late potentials after coronary bypass surgery.

The detection of frequent or complex, or both, ventricular ectopic beats on a predischarge Holter recording represents an independent prognostic factor for late arrhythmic events after AMI.[23-26] Some studies[11,12,15,27] evaluated the influence of reperfusion and thrombolytic therapy on late ventricular ectopic activity; the results were controversial. We used maximal exercise testing and Holter monitoring to evaluate the ventricular ectopic activity in our patients. The majority of patients underwent 48-hour recording for better detection of complex ventricular arrhythmias (couplets and ventricular tachycardia). We did not find any significant difference in both frequency and complexity of ventricular ectopic beats between patients treated with thrombolysis and control subjects. Furthermore, late ventricular ectopic activity was not significantly different between patients with and without patency of the infarct-related coronary artery.

In the follow-up studies we found that late potentials were significantly related to late arrhythmic events. Several investigators[4-8] evaluated the prognostic significance of late potentials; in these studies it was not mentioned how many patients received thrombolysis. Furthermore, most of these studies were performed before the extensive use of fibrinolytic therapy. We analyzed the possible influence of thrombolysis on the predictive ability of late potentials for a post-AMI arrhythmic event, as suggested in a recent editorial[16]; also, in the group of 99 patients treated with thrombolysis, late potentials were significantly related to late arrhythmic events. Therefore, detection of late potentials is a useful marker of future malignant ventricular tachyarrhythmias after thrombolytic therapy.

We evaluated a possible difference in arrhythmic event rate between patients treated with and without thrombolysis in both the general population of the study and the group with anterior wall AMI and left ventricular dyskinesia (higher event rate). We did not observe any significant difference; in any case there was a significantly higher relative risk of developing arrhythmic events in the conventionally-treated group. The small number of arrhythmic events and the short follow-up prevent us from advancing conclusions.

An extremely low mortality rate was observed in patients with reperfusion compared with in those without.[1] This finding contrasts strikingly with the relatively modest changes in left ventricular function observed between the 2 groups of patients. Conversely, a significant difference in the rate of late potentials is appreciable in both reperfused patients and those treated with thrombolysis.[9,10,12-15] Our data are in agreement with these findings. Moreover, in agreement with other studies,[4-8] late potentials were significantly related to late arrhythmic events, and several investigators[5,7,8] have found late potentials to be independent predictors of malignant ventricular tachyarrhythmias after AMI. The mechanism responsible for reduced mortality after fibrinolysis has not yet been examined.[28] The results of this and other studies strongly suggest increased electrical heart stability as a potential mechanism for the improvement in prognosis after thrombolysis. The prevention of the development of an arrhythmogenic substrate in reperfused patients could have an important role in increasing survival after AMI.

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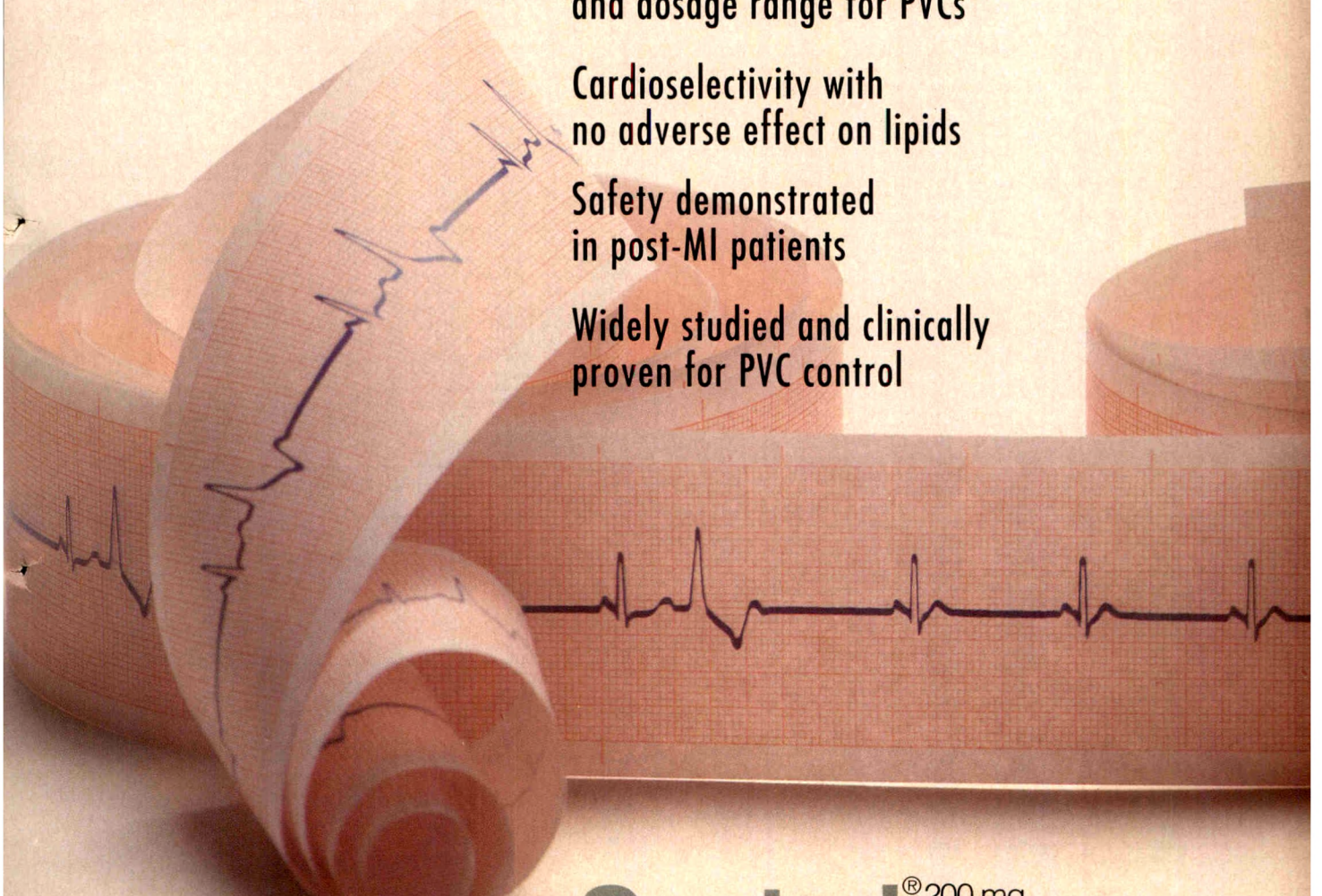
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THE CARDIOSELECTIVE BETA BLOCKER FOR PVC CONTROL

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THE CARDIOSELECTIVE BETA BLOCKER FOR PVC CONTROL

Usual starting dose	**200 mg b.i.d.**
Optimal PVC response	**600 mg to 1200 mg per day**
Use in elderly	**Doses above 800 mg per day should be avoided**

(Brief Summary. See Package Circular for full prescribing information.)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium, use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{Cr}); reduce daily dose of acebutolol by 50% when Cl_{Cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N = 1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous. Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

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Cardiopulmonary Receptor and Arterial Baroreceptor Reflexes After Acute Myocardial Infarction

Guido Grassi, MD, Cristina Giannattasio, MD, Gino Seravalle, MD, Giuseppe Osculati, MD, Franco Valagussa, MD, Alberto Zanchetti, MD, and Giuseppe Mancia, MD

The baroreceptor–heart rate reflex in human is impaired 2 days after a myocardial infarction but it improves 10 days after the acute coronary event. This study investigated whether (1) the baroreceptor–heart rate reflex improvement takes the reflex back to normal, and (2) the cardiopulmonary reflex is affected by myocardial infarction. In subjects studied 8 to 11 days after a transmural anterior or inferior myocardial infarction the baroreceptor–heart rate reflex sensitivity (slope of the linear regression between negative neck chamber pressures and lengthenings in RR interval) was similar to that seen in control subjects (−6.2 ± 0.8 vs −6.0 ± 0.6 ms/mm Hg, mean ± SEM) and did not change when reassessed 10 days later. In contrast, the cardiopulmonary reflex sensitivity (changes in forearm vascular resistance induced by changing central venous pressure through non-hypotensive lower body suction and leg raising) was markedly less in subjects studied 8 to 11 days after myocardial infarction than in control subjects; the reduction amounted to 58.1 ± 8% ($p < 0.01$). The cardiopulmonary reflex sensitivity greatly improved when reassessed 28 to 45 days later. Thus, the baroreflex is normal about 10 days after myocardial infarction. This condition markedly impairs the cardiopulmonary reflex, but the impairment is also transient.

(Am J Cardiol 1992;69:873–878)

We have previously shown that arterial baroreceptor modulation of heart rate in humans is markedly impaired 2 days after an acute myocardial infarction but improves considerably about 10 days after the acute coronary event.[1] In the present study we addressed 2 issues that had not been previously clarified: (1) whether the arterial baroreflex is entirely normalized after the acute post–myocardial infarction phase, the potentially adverse consequences of its impairment (e.g., increased sympathetic and reduced vagal drive) being thus largely short term; and (2) whether the cardiopulmonary receptor reflex[2] is also impaired after myocardial infarction, as it is suggested by animal studies.[3] The latter is an important issue because the cardiopulmonary receptor reflex in humans originates mainly from the heart[4,5] and modulates systemic vascular resistance, plasma catecholamines and plasma renin activity,[6–8] i.e., variables undergoing a derangement in the post–myocardial infarction phase.[9–11]

METHODS

We studied 35 patients of both sexes (31 men and 4 women), who were admitted to the coronary care unit of our hospital for an acute transmural myocardial infarction either of the anterior or the inferior wall. Myocardial infarction was diagnosed by a history of prolonged (>1 hour) chest pain and by standard electrocardiographic and laboratory criteria. No patient had evidence of a previous myocardial infarction, and none had a history of high blood pressure, diabetes, autonomic neuropathy, renal damage or other major cardiovascular diseases. The presence of heart failure was excluded by the absence of breathlessness, pulmonary rales, third heart sound and signs of pulmonary hypertension and cardiac enlargement on chest radiography. Left ventricular end-diastolic diameter measured by echocardiography was always <55 mm. When admitted to the coronary care unit, patients with myocardial infarction received morphine sulphate, intravenous nitroglycerin, streptokinase or heparin, or a combination of these. Calcium antagonists, β blockers and nitrates were given accordingly to the clinical needs but, with the exception of aspirin, drugs with major cardiovascular action were withdrawn during the 48 hours preceding the first or second baroreflex and cardiopulmonary reflex study (see later).

Thirty-four hospitalized patients of either sex were taken as control subjects. The subjects were selected if there were no major systemic and cardiovascular diseases and if there was none of the aforementioned con-

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ditions affecting autonomic cardiovascular control. All subjects gave their informed consent to the study and the protocol was approved by the ethical committee of our institution.

Evaluation of the carotid baroreflex: The carotid baroreceptor control of heart rate was studied by the neck chamber technique that allows one to produce a negative pressure around the neck, increasing carotid transmural pressure and selectively stimulating carotid baroreceptors.[12,13] The study was performed in 30 patients with a myocardial infarction (age 52 ± 1 year, range 41 to 64) and in 24 control subjects (age 50 ± 1 year, range 39 to 64) 8 to 11 days after the coronary event and the hospitalization (mean 10 ± 1 and 10 ± 1 days), respectively, and after 1 week of mobilization in the semi-intensive care ward. In 24 patients with myocardial infarction, the baroreflex was reassessed 18 to 22 days (mean 21 ± 1) after the coronary event and following discharge from the hospital without any physical rehabilitation program. In each experimental session the negative pressure was applied in 6 separate steps of 10-second duration, ranging in magnitude from −7 to −40 mm Hg. Each step was repeated 3 times and the steps were applied in a random order and separated from each other by 2 minutes. Baroreceptor deactivation by positive neck chamber pressure was not pursued because the procedure was disturbing to the patients.

During the experimental session, the pressure within the collar was measured by a Statham transducer (model P23 ID, Gould Statham, Hato Rey, Puerto Rico). Blood pressure was measured by a sphygmomanometer using the first and fifth Korotkoff sounds to identify systolic and diastolic blood pressure, respectively. Heart rate was measured by a cardiotachometer triggered by the R wave of an electrocardiographic lead. The neck pressure and heart rate signals were recorded on a Grass Polygraph (Grass Instruments, Quincy, Massachusetts), which also displayed the electrocardiographic signal to allow precise measurements of the RR interval.

Evaluation of the cardiopulmonary reflex: Cardiopulmonary receptors were (1) stimulated by increasing central venous pressure through passive elevation of legs to 60°[2]; and (2) deactivated by reducing central venous pressure through application, with a lower body negative device, of a negative pressure so mild (approximately −15 mm Hg) as to have little effect on blood pressure and heart rate and thus modify arterial baroreceptor activity to only a minor degree.[2] A more marked lower body negative pressure was also applied (approximately −35 mm Hg) to cause a reduction in blood pressure, deactivate both cardiopulmonary and arterial baroreceptors and thus simulate the concomitant engagement of these homeostatic mechanisms in physiological conditions (e.g., orthostatic stress). The study was performed in 12 patients with myocardial infarction (aged 52 ± 2 years, range 34 to 63) and in 12 control subjects (aged 50 ± 2 years, range 39 to 65) 9 to 13 days after the acute coronary event and hospitalization (mean 11 ± 1 and 10 ± 1 days), respectively, and after 1 week of mobilization in the semintensive care ward. In 7 patients with myocardial infarction, the cardiopulmonary reflex was reassessed 28 to 45 days (mean 37 ± 10) after the coronary event and following discharge from the hospital without any physical rehabilitation program. In each experimental session the stimuli were applied randomly and maintained for 5 minutes. Each stimulus was separated from the preceding one by a 10-minute interval. Seven patients with myocardial infarction and 7 control patients also participated in the baroreflex study.

During the experimental session arterial blood pressure and heart rate were measured as described for the baroreflex study. The pressure within the box was measured by a Statham transducer (P23 ID, Gould Statham, Hato Rey, Puerto Rico). Central venous pressure was measured by a catheter placed in or near the right atrium from an antecubital vein of the arm used for blood pressure measurements and also connected to a Statham transducer. Forearm blood flow was measured by venous occlusion plethysmography (Hokanson EC4, Issaqua, Washington), using the forearm other than that measured for blood pressure. The measurements were performed as described in previous studies.[4,5,7,8] Forearm vascular resistance was derived from the ratio between mean arterial pressure (diastolic blood pressure plus ⅓ third of pulse pressure) and forearm blood blow. Blood pressure, heart rate, forearm blood flow and forearm vascular resistance were measured also before and during 1-minute immersion of 1 hand in ice water (4°C) to determine the hemodynamic responses to a neurogenic stimulus different from that originating from cardiopulmonary receptors.

Data were calculated by an investigator unaware of the experimental design. Baseline values were obtained by averaging the measurements before the various stimuli. The response to neck pressure application was calculated by taking the maximal lengthening of RR interval over the 3 beats following the onset of the stimulus, i.e. over a time interval still devoid of blood pressure effects.[14] Data from the 3 stimuli of similar magnitude were averaged and the slope of the linear regression of RR interval on neck pressure changes was taken as the carotid baroreflex sensitivity. The response to lower body negative pressure, leg raising and cold pressor test was calculated by taking the values of the last minute of the stimulus. Forearm blood flow (and vascular resistance) was always derived from the average of 3 consecutive values.

Individual data were averaged separately for the patients with myocardial infarction and control subjects to obtain the means (± SE) for the 2 groups. The differences between mean data were analyzed by the *t* test for unpaired (myocardial infarction vs control patients) or paired (first vs second study) observations. Relationships between variables were assessed by linear regression analysis. A p value <0.05 was taken as the level of statistical significance.

RESULTS

Carotid baroreflex: Ten days after hospitalization, baseline mean arterial pressure was slightly lower in pa-

tients with myocardial infarction than in control subjects, whereas baseline RR interval was not significantly different in the 2 groups (Figure 1). Baroreflex sensitivity was similar in patients with myocardial infarction and in control subjects, and in the subgroups with an anterior and inferior myocardial infarction (−6.4 ± 1.5 vs −6.2 ± 1.1 ms/mm Hg, data not shown in Figure). No correlation was found between the baroreflex sensitivity and the creatinine phosphokinase-MB values taken as an approximate index of the size of myocardial infarction (r = 0.20, p = not significant). Figure 1 compares the results obtained 10 and 21 days after myocardial infarction. Baseline RR interval increased slightly over this time, whereas baseline mean arterial pressure remained unchanged. The individual baroreflex sensitivity observed 10 days after myocardial infarction was

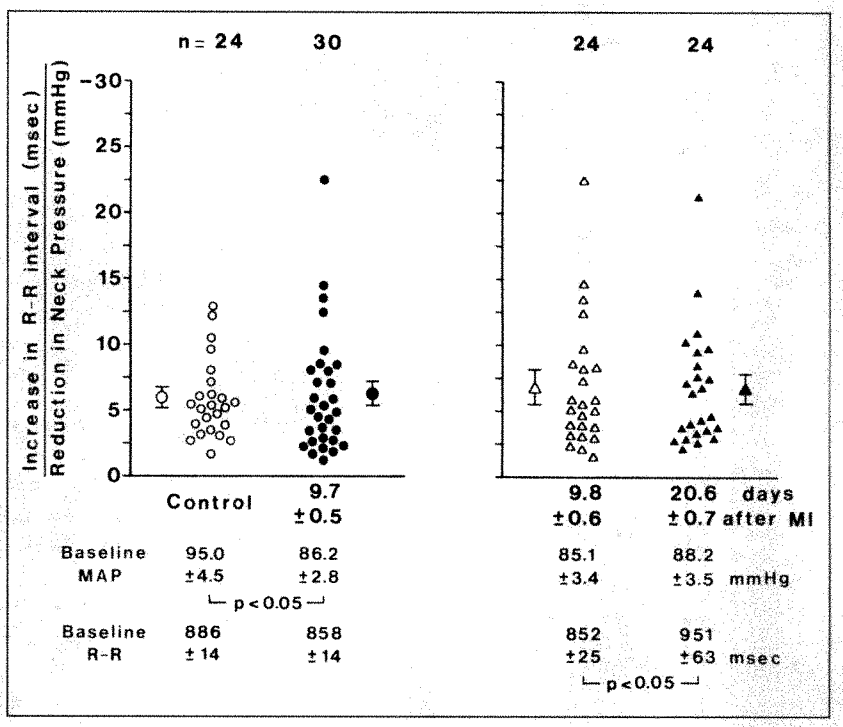


FIGURE 1. ***Left panel,*** **individual and average baroreflex sensitivities in patients with myocardial infarction (MI, *closed circles*) studied 9.7 ± 0.5 days after the coronary event and in control subjects (*open circles*) studied 9.6 ± 0.7 days after hospitalization. *Right panel,* individual and average baroreflex sensitivities in patients studied both at the earlier (*open triangles*) and at a later (*closed triangles*) phase after myocardial infarction. Baseline mean arterial pressure (MAP) and RR interval values are also shown. Note that baroreflex sensitivity is negative because a reduction in neck pressure was accompanied by an increase in RR interval.**

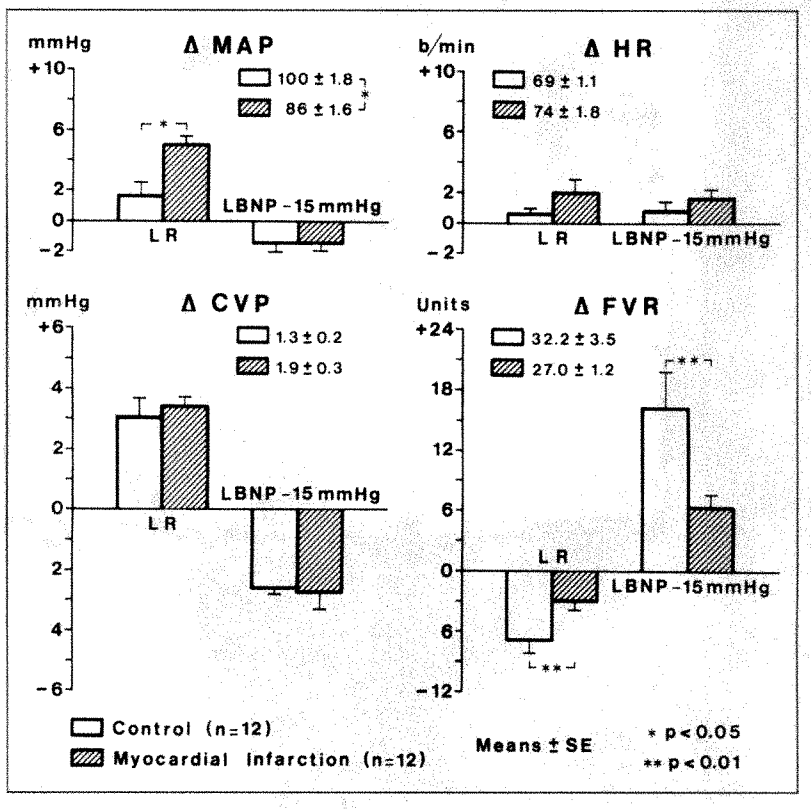


FIGURE 2. Changes in mean arterial pressure (ΔMAP), heart rate (ΔHR), central venous pressure (ΔCVP) and forearm vascular resistance (ΔFVR) induced by leg raising (LR) and lower body negative pressure (LBNP) −15 mm Hg in 12 patients studied 11 ± 1 days after a myocardial infarction. Data from 12 control subjects studied 10 ± 1 day after hospitalization are also reported. *Numbers* shown in each panel refer to baseline values.

TABLE I Hemodynamic Changes Induced by Lower Body Negative Pressure at −35 mm Hg

	C (n = 12)	MI (n = 12)	MI (11 ± 1 days) (n = 7)	MI (37 ± 10 days) (n = 7)
CVP (mm Hg)	−3.8 ± 0.4	−3.9 ± 0.5	−3.0 ± 0.4	−3.3 ± 0.4
MAP (mm Hg)	−5.2 ± 0.6	−5.8 ± 0.7	−6.5 ± 1.1	−2.4 ± 0.8 *
HR (beats/min)	+7.8 ± 1.6	+7.4 ± 1.6	+8.7 ± 1.5	+7.2 ± 1.3
FVR (U)	+20.6 ± 4.5 *	+8.3 ± 1.6	+10.7 ± 2.6 *	+18.7 ± 4.8

*$p < 0.05$.
Values are mean ± SE.
C = control subjects; CVP = central venous pressure; FVR = forearm vascular resistance; HR = heart rate; MAP = mean arterial pressure; MI = myocardial infarction.

closely correlated with that observed in the later phase ($r = 0.83$, $p < 0.001$) and the average baroreflex sensitivity was virtually identical in the 2 circumstances.

Cardiopulmonary receptor reflex: Eleven days after hospitalization, baseline mean arterial pressure was slightly lower, and baseline forearm vascular resistance slightly higher in patients with myocardial infarction than in control subjects (Figure 2). Baseline heart rate and central venous pressure were not statistically different in the 2 groups. Figure 2 also shows that in control subjects, leg raising and lower body negative pressure at −15 mm Hg caused an increase and a reduction, respectively, in central venous pressure. Mean arterial pressure and heart rate exhibited small and nonsignificant changes, whereas forearm vascular resistance decreased with the former maneuver and markedly increased with the latter. In patients with myocardial infarction the changes in central venous pressure were similar to those seen in control subjects, again with little heart rate changes and with similar or slightly greater blood pressure changes for leg raising. Compared with control subjects, both the decrease and increase in forearm vascular resistance in patients with myocardial infarction were markedly reduced. Figure 3 compares the results obtained about 11 and 37 days after MI. Baseline central venous pressure, mean arterial pressure and heart rate remained unchanged over this time, whereas baseline forearm vascular resistance decreased. The effects of leg raising and lower body negative pressure at −15 mm Hg on central venous pressure, mean arterial pressure and heart rate were similar in the 2 circumstances. In contrast, the reduction and increase in forearm vascular resistance were much greater at 37 days than in the earlier phase after myocardial infarction.

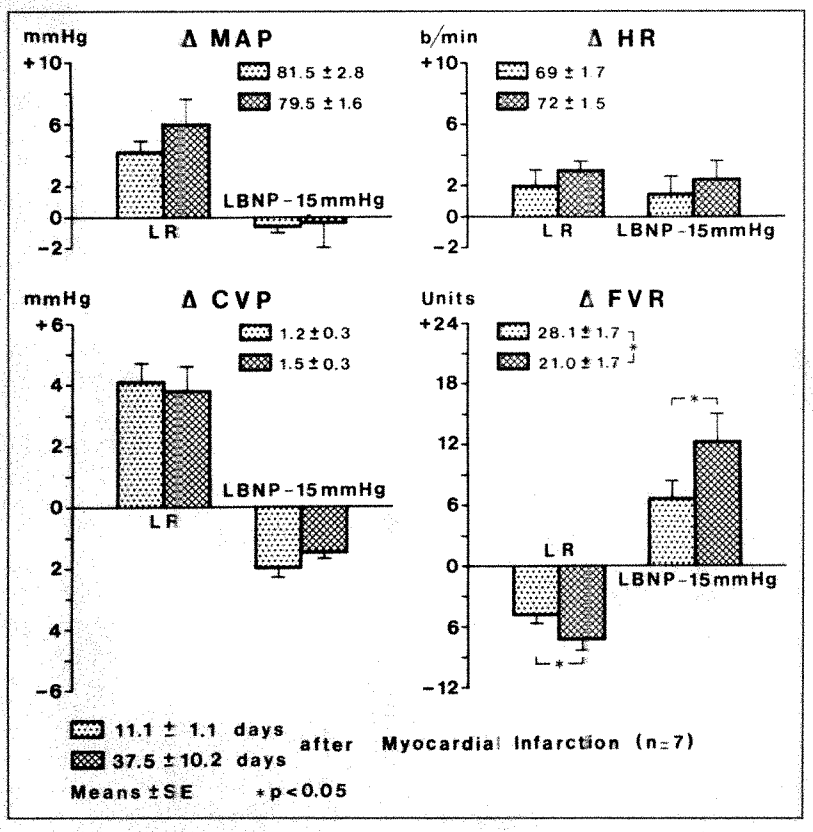


FIGURE 3. Mean ± SE changes in mean arterial pressure (ΔMAP), heart rate (ΔHR), central venous pressure (ΔCVP), and forearm vascular resistance (ΔFVR) induced by leg raising (LR) and lower body negative pressure (LBNP) − 15 mm Hg in 7 patients studied at an earlier and later phase after myocardial infarction.

Hypotensive lower body negative pressure: Eleven days after hospitalization lower body negative pressure at −35 mm Hg caused a decrease in central venous pressure greater than that observed when the same stimulus was applied at −15 mm Hg (Table I and Figure 2). This was accompanied by a decrease in blood pressure and an increase in heart rate and forearm vascular resistance. The reduction in central venous pressure, the hypotension and the tachycardia were similar in patients with myocardial infarction and in control subjects. Subjects with myocardial infarction however, displayed a large attenuation of the forearm vascular resistance response. Also this response improved when the lower body negative pressure at −35 mm Hg was applied 37 days after myocardial infarction. This was accompanied by less hypotension but by a similar tachycardic response.

Cold pressor test: Ten days after myocardial infarction, immersion of 1 hand in ice water was associated with a marked increase in mean arterial pressure, a moderate tachycardia and a marked increase in forearm vascular resistance. All changes were similar to those seen in control subjects (mean arterial pressure: patients with myocardial infarction, +14.1 ± 1.5 mm Hg; control subjects, +13.3 ± 1.2 mm Hg; heart rate: myocardial infarction, +10.4 ± 1.9 beats/min; controls, +9.3 ± 1.0 beats/min; forearm vascular resistance: myocardial infarction, +24.8 ± 5.8 U; controls, +23.9 ± 6.1 U).

DISCUSSION

In the present study a reduction in central venous pressure was accompanied by much less increase in forearm vascular resistance in patients with an 11-day-old transmural myocardial infarction than in control subjects. Furthermore, an increase in central venous pressure was accompanied by less reduction in forearm vascular resistance in those with myocardial infarction than in control subjects. The reduction in central venous pressure was always devoid of significant blood pressure and heart rate changes, and the increase in central venous pressure was devoid of significant heart rate changes and accompanied by a small although significant blood pressure increase only in patients with myocardial infarction. This rules out the possibility that during the changes in central venous pressure the reduced vascular responses in patients with myocardial infarction were accounted for by the arterial baroreflex. Thus, one can conclude that this was due to an impairment of the cardiopulmonary reflex. This represents the first evidence of this phenomenon in humans.

We have previously reported that the impaired baroreceptor–heart rate reflex seen 2 days after a transmural myocardial infarction undergoes a clear improvement 10 days after the coronary event.[1] Our present study offers 3 additional findings. (1) In a large number of patients studied 10 days after myocardial infarction, the bradycardic responses to several different carotid baroreceptor stimuli were similar to those obtained in a large number of control subjects. (2) Another response originating from arterial baroreceptor deactivation, i.e., the tachycardia accompanying a lower body negative pressure marked as to induce hypotension,[2,13] was indistinguishable in the 2 groups. (3) The reflex bradycardic and tachycardic responses observed 10 days after myocardial infarction were unchanged at a later time, indicating that the normal baroreflex sensitivity of patients with myocardial infarction was thereafter fully maintained. A second conclusion of our study is that the myocardial infarction–dependent impairment of the baroreceptor–heart rate reflex previously described[1] is a transient phenomenon and that the improvement occurring 10 days after myocardial infarction is pronounced so as to allow this mechanism to recover steadily normal values. Recovery from impairment after myocardial infarction is not specific for the baroreceptor–heart rate reflex because the cardiopulmonary receptor reflex of our patients with myocardial infarction also exhibited a marked improvement from the initial impairment, although over a slower time course.

Our study does not clarify the mechanisms responsible for the impairment of the cardiopulmonary receptor reflex after myocardial infarction. However, a nonspecific depression of vascular responsiveness to neural stimuli can be ruled out because the hemodynamic effects of cold pressor testing were normal in patients with myocardial infarction at the time when the responses to cardiopulmonary receptor manipulation were reduced. Thus, the reflex impairment originates either centrally or in the afferent component of the reflex arch, or both. We can speculate that the afferent impairment depends on (1) a destruction of receptors located in the necrotic area; (2) a reduction in cardiac compliance that, dealing with stretch receptors, would cause fewer changes in receptor activity for a given increase and decrease in central venous pressure; and (3) a receptor abnormality induced by ischemia (e.g., receptor stunning), dyskinesia or exhaustion after an earlier massive excitation.[15] Regardless of its nature, however, it is clear that the impairment should be reversible to account for the later recovery of the cardiopulmonary receptor reflex. In principle, this phenomenon may occur even with a necrotic destruction of cardiac receptors because neural plasticity may allow the remaining receptors to assume greater importance with time.

Schwartz et al[16] reported that the bradycardia accompanying the sustained and progressive increase in blood pressure induced by intravenous infusions of increasing doses of phenylephrine was reduced in a number of patients studied 18 days after myocardial infarction. However, a sustained blood pressure increase may stimulate cardiac receptors through an increase in left ventricular diastolic pressure,[17] i.e., a change that can easily occur when an altered cardiac pump can cope less effectively with an increased afterload. It is thus possible that the late baroreflex impairment reported by Schwartz et al[16] in a number of subjects with myocardial infarction reflects the impairment of the cardiopulmonary receptor reflex.

Our findings have clinical implications because the cardiopulmonary reflex exerts an important restraint on sympathetic activity and thus on (1) norepinephrine and epinephrine release from the nerve terminals,[7] (2) renin release from the juxtaglomerular cells,[8] and (3) system-

ic vascular resistance[6] and coronary vasomotor tone.[18] Its impairment can thus contribute to the marked increase in plasma catecholamines and renin activity that occurs in the phase after myocardial infarction and to the adverse impact this has on the patient's prognosis.[19–22] It can also adversely affect cardiac function by increasing cardiac afterload while reducing cardiac perfusion.

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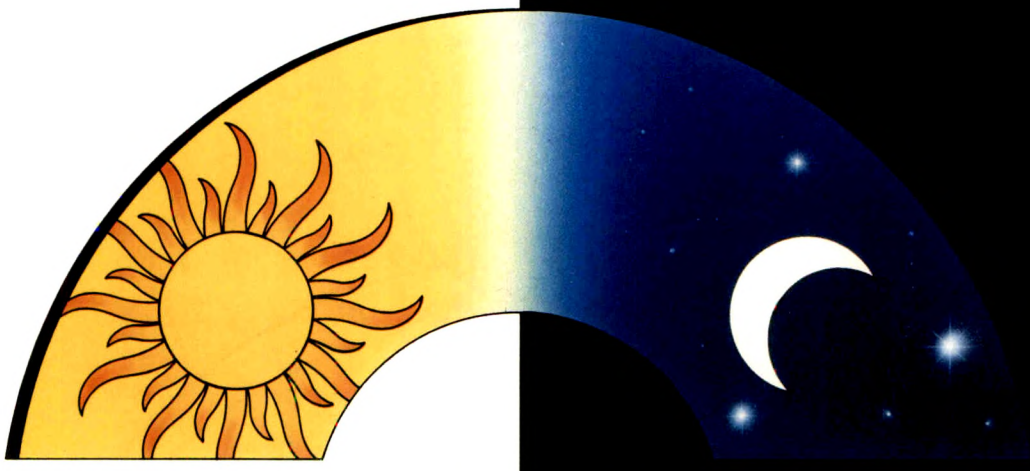
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ALL DAY ALL NIGHT

ALTACE™

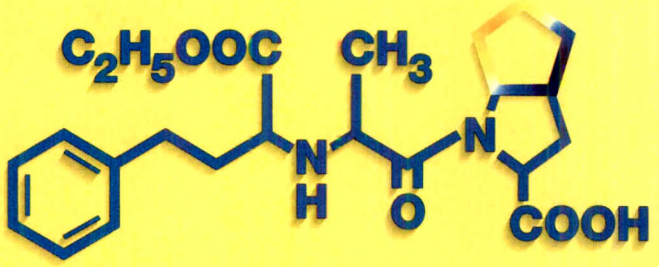
ramipril

24-HOUR BLOOD PRESSURE CONTROL

Please see brief summary of prescribing information on last page.

ALL DAY

Unique Cyclopentane Ring for Distinctive Pharmacology



Longest serum half-life

13 to 17 hours

High ACE affinity

Binds readily to enzyme and dissociates slowly[1]

Enhanced tissue penetration

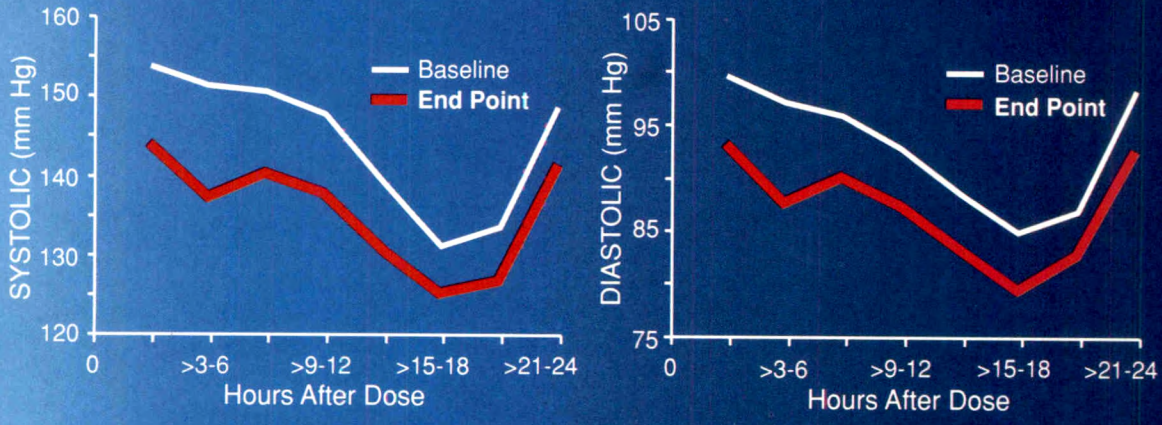
Markedly reduced ACE activity in both human serum and tissue for effective blood pressure control[2]

* In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval.

Please see brief summary of prescribing information on last page.

ALL NIGHT

24-Hour Blood Pressure Control with a Once-a-Day Dose*



Mean 24-hour ambulatory blood pressures in 67 patients at baseline and after 4 weeks of therapy. (Adapted from McCarron.[3])

Usual starting dose—
2.5 mg once-a-day

ALTACE™
ramipril

ALL DAY/ALL NIGHT

ALTACE™ ramipril

Available in Easy-to-Swallow Capsules



1.25 mg 2.5 mg 5 mg 10 mg

Usual Starting Dose–2.5 mg Once-a-Day

BRIEF SUMMARY

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE should be discontinued as soon as possible. **See WARNINGS: Fetal/neonatal morbidity and mortality.**

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in color-coded, hard gelatin capsules.

INDICATIONS AND USAGE: ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS: ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with history of angioneurotic edema.

WARNINGS: ***Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision; they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. More than 100 cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible and irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examination should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be apparent until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE, which crosses the placenta, can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a mg/kg basis, the doses used were up to 2,500 times (in rats), 6.25 times (in rabbits), and 1,250 times (in monkeys) the maximum recommended human dose.

PRECAUTIONS: ***General:*** *Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTACE. (See DRUG INTERACTIONS.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE™ (ramipril) should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should also be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *With Diuretics:* Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced.

With Potassium Supplements and Potassium-Sparing Diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, or antacid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats (up to 500 mg/kg/day for 24 months) or to mice (up to 1,000 mg/kg/day for 18 months). Dosages greatly in excess of those recommended for humans produced hypertrophy of the renal juxtaglomerular apparatus in mice, rats, dogs, and monkeys. No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy: **Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS: Fetal/neonatal morbidity and mortality.**

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Geriatric Use: Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS: ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE are shown below.

PATIENTS IN US PLACEBO-CONTROLLED STUDIES

	Altace (N = 651)		Placebo (N = 286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment. Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following. (In some, a causal relationship to drug use is uncertain.):

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (see PRECAUTIONS and WARNINGS), syncope (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, and cerebrovascular events.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See WARNINGS.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment. (See PRECAUTIONS.)

Gastrointestinal: Abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste disturbance, and vomiting.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash, with or without fever), photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS: Fetal/neonatal morbidity and mortality.

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings: *Creatinine and Blood Urea Nitrogen:* Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See PRECAUTIONS and WARNINGS.)

Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See PRECAUTIONS and WARNINGS.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE: Human overdoses of ramipril have not been reported, but the most common manifestation of human ramipril overdosage is likely to be hypotension. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

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An Indian Experiment with Nutritional Modulation in Acute Myocardial Infarction

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In a randomized, single-blind intervention trial, 406 patients 24 to 48 hours after acute myocardial infarction (AMI) were assigned to either diet A (204 patients, group A) or B (202 patients, group B) for 6 weeks. At entry to the study, mean age, male sex, risk factors, complications, possible and definite AMI, and drug therapy were comparable between the 2 groups. Dietary adherence to intervention and control diets was checked by questionnaire, and drug therapy by tablet count. Group A received significantly lower calories, a higher percentage of calories from complex carbohydrates, vegetable/fish proteins, polyunsaturated fatty acids, and a higher polyunsaturated/saturated fat ratio diet than did group B (higher total calories and saturated fatty acids). Group A also received less dietary cholesterol, salt and caffeine, and higher soluble dietary fiber, vitamins and minerals than did group B. After 6 weeks, group A had a significant decrease in mean serum total (−20.5 vs −8.6 mg/dl) and low-density lipoprotein (−16.6 vs −6.4 mg/dl) cholesterols, and triglycerides (−15.5 vs −7.6 mg/dl), with no decrease in high-density lipoprotein cholesterol (−1.5 vs −1.3 mg/dl) compared with the initial levels and changes in group B. Group A also had a greater decrease in mean body weight (3.4 vs 1.3 kg) than that of group B. A significant decrease in body weight and better modulation of blood lipids in group A were translated into a significant decrease (34.5%) in total cardiac end points including nonfatal (17 vs 25) and fatal (8 vs 12) AMI, and sudden cardiac death (4 vs 7) compared with that in group B (29 vs 44, $p < 0.01$, 2-tailed). Total mortality, including cardiac mortality (12 vs 21), showed no significant difference between groups A and B during 6-week follow-up. This needs further confirmation owing to the small number of events.

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Recurrent acute myocardial infarction (AMI) and death are frequent outcomes in patients with AMI. The mortality rate during hospitalization is 10 to 15%, and the rate of reinfarction or extent of infarction may be 10 to 30% depending on the criteria used for diagnosis.[1,2] Whereas the majority of the deaths are due to arrhythmias, coronary artery stenosis may be the cause of ischemia and reinfarction.[1,2] There is evidence that hyperlipidemia can inhibit the secretion of the endothelial-dependent relaxant factor,[3] and predispose thrombosis and atherosclerosis,[4] and that reduction of blood lipids may be associated with a significant decrease in nonfatal AMI.[5–8] Recently, increased intake of fish in patients after AMI was demonstrated to cause a significant decrease in heart disease and all-cause mortality.[9] There is evidence that several common Indian foods[10–16] such as onion, garlic, guava, stargooseberry, fenugreek seeds, mushrooms, black, red and bangal grams, trichosanthes, bitter gourd, soya beans, oils of ground nut, soya bean and sun flower, almonds and walnuts can modulate blood lipids and sugar, and fibrinolytic activity leading to a decrease in atherosclerosis.[10–18] The clinical effects of a diet rich in these foods may be similar to those of taking 180 mg/day of aspirin.[19] In 1 preliminary study[20] we documented for the first time that a diet rich in these foods given to patients with AMI can have a beneficial influence on complications and mortality. In the present study, we reexamined the influence of this cardiovasoprotective diet rich in fruits, vegetables, cereals, nuts and fish for confirmation of previous findings.

METHODS

All patients admitted to the hospital with a clinical diagnosis of suspected AMI within 24 hours were considered for the study. The criterion[21] of diagnosis of AMI was a 12-lead electrocardiogram showing symmetrical ST-segment depression or elevation of ≥ 1 mm from baseline in limb leads or of ≥ 2 mm in chest leads, or T-wave inversions with or without Q waves in association with an increase in creatine phosphokinase and serum glutamic oxalotransferase of at least twice the normal values on serial examination, or a combination. Suspected AMI was diagnosed by presence of convincing history of cardiac chest pain accompanied by less than twice the increase in enzymes of normal values, electrocardiographic abnormalities that were not diagnostic of AMI, ischemic heart disease by chest pain without an increase in enzymes, or absence of diagnostic electrocardiographic changes, or a combination. Exclusion criteria are given later (see Results). Patients were observed for 24 hours after the clinical diagno-

sis of AMI, during which dietary intake, drug therapy and complications were recorded. Clinical, electrocardiographic, radiologic and laboratory data were also obtained for all patients during this period.

Blood pressures were measured after 5 minutes of rest (lying comfortably in a supine position) by a mercury sphygmomanometer by 1 technician. Korotkoff sounds phase V was recorded for diastolic blood pressure. Hypertension was diagnosed as blood pressure >150/95 mm Hg, diabetes mellitus as a positive glucose tolerance test showing >140 mg/dl after 2 hours of 75 g of oral glucose, smoking as consumption of ≥1 cigarette/day, obesity as >10% above normal weight for age and sex, hypercholesterolemia as fasting serum cholesterol >250 mg/dl, hypertriglyceridemia as fasting serum triglycerides >190 mg/dl, physical inactivity as <1 km/day of walking during routine work without any exercise, and alcohol intake as >60 g/week of alcohol.

Study design: After giving written informed consent, all patients with the suspected clinical diagnosis of AMI were randomized by the dietitian and assigned a diet by blindly selecting a card designated diet A or B from a stack with an equal number of each, and the responsible physician was unaware of the assigned dietary regimen. All patients remained in the hospital for 10 to 30 days.

In the intervention diet, meat and eggs were replaced with fish, vegetarian meat substitutes and nuts to keep the diet low in saturated fat. Small, frequent meals (200 to 300 Kcal, 5 to 6 times daily) in the form of a soft diet such as soup (especially in the first week) containing fruits, vegetables, cereals and nuts (in particular, almonds, walnuts, guava, stargooseberries, grapes, apples, sweet limes, bananas, lemons, raisins, bail, musk melons, onions, garlic, trichosanthes, fenugreek seeds and leaves, mushrooms, bitter and bottle gourds, lotus roots, bengal and black grams, soya beans, green leafy vegetables, and oils of soyabean and sun flower) were regularly advised in group A patients. Group B patients were administered a low-caloric, typical diet during hospitalization, and later were on a diet as prescribed by their doctor. Dietary intake before hospitalization was also obtained in both groups by obtaining the food intake of spouses, and detailed history of food intake of all patients.

All patients completed angina pectoris record (including daily trinitrate consumption and intake of other drugs) and dietary diaries with the help of the dietitian, beginning at days 3, 6 and 10, and then weekly for 6 weeks to verify dietary and drug compliance (by tablet count). Dietary compliance was checked and reinforced daily during hospitalization (10 to 30 days) by the dietitian. Each patient was counseled regularly at separate counseling sessions and was asked to answer a questionnaire concerning dietary intake, smoking, and alcohol and drug intake to enforce drug and dietary compliance, and to stop or reduce smoking and alcohol intake in both groups. General measures such as physical activity, maintenance of regular bowel movements and counseling for mental stress were actively performed in both groups depending on complications and clinical indications. Nutrient intake was calculated by computation of Indian food composition tables[22] based on the questionnaire regarding dietary adherence by 24-hour recall.

Data collection: Clinical data, complications, drug therapy and mortality were regularly recorded for 6 weeks by the physician unaware of the dietary regimens in both groups. Blood pressure and heart rate were recorded in the right arm twice daily during hospitalization, and then weekly after 5 minutes of rest in the supine position, and phase V of Korotkoff sounds was recorded as diastolic blood pressure. Systolic blood pressure <90 mm Hg was described as hypotension. A 12-lead electrocardiogram was obtained daily for the first 4 to 5 days, then every third day and when indicated during hospitalization, and after discharge, once weekly at every visit to the clinic. Heart rate was calculated from the resting electrocardiogram, and left ventricular strain by ST-segment depression or T-wave inversion, or both, in leads V_5-V_6. Angina was treated (and recorded through angina diaries) when chest pain persisted for >3 minutes disappearing or diminishing on taking sublingual nitroglycerin. Arrhythmias were diagnosed by electrocardiogram and 24-hour monitoring, and treated in presence of ventricular ectopics (minimum 8 beats/min) that may be uni- or multifocal, or >3 consecutively. Heart failure was recorded on the basis of the criteria of the New York Heart Association as a dilated heart, demonstrated by radiologic or electrocardiographic (or both) dilatation of the left ventricle. Heart enlargement was considered as a dilated heart demonstrated by radiologic or electrocardiographic examination, or both. The diagnosis of cardiovascular complications and end points was based on earlier criteria.[21]

Fatal AMI was diagnosed when the hospital record was consistent with the cause of death and there was either preterminal hospitalization with or a record showing definite AMI. Sudden cardiac death was diagnosed in the case of a record describing AMI or ischemia, and death occurring within 1 hour of the onset of symptoms. Suspected cardiac death was considered in the case of a death certificate describing coronary disease without evidence suggestive of sudden cardiac death. In hospitalized patients, nonfatal AMI was diagnosed as a diagnostic electrocardiogram recorded at the time of the event (as mentioned previously)[23] or ischemic cardiac pain, and diagnostic enzyme levels of either creatine phosphokinase, lactate dehydrogenase or serum glutamic oxalotransferase more than twice the higher limit of normal levels. Possible or suspected AMI was considered as ischemic cardiac pain with equivocal enzyme levels and electrocardiogram. The diagnosis of AMI was also considered in nonhospitalized patients with a record showing indefinite history of AMI and with a diagnostic electrocardiogram at the time of the event, or new electrocardiographic changes with increased enzymes consistent with AMI observed during routine checkup. Minnesota coding of the electrocardiogram was performed by a cardiologist who had no clinical information concerning the patients. Possible AMI was considered as a coronary event, but not as a final cardiovascular end point.

Laboratory data were obtained at entry to the study and after 6 weeks in all patients. A venous blood sample was obtained in a fasting state and analyzed for blood count, hemoglobin, urea, glucose, cardiac enzyme activity, total cholesterol,[24] high- and low-density lipoprotein cholesterols, triglycerides[23] and electrolytes in all patients. Total cholesterol was measured directly in the serum, and high-density lipoprotein cholesterol was measured after precipitation of very low-density and low-density lipoproteins by an enzymatic method.[24] Serum glutamic oxalotransferase and creatine phosphokinase were obtained at entry to the study, and 48 and 72 hours after AMI, and lactate dehydrogenase on the sixth or seventh day after AMI.

Data were analyzed on the basis of intention to treat, and in all outcome analyses during follow-up, the last available clinical or laboratory data were incorporated for patients who were lost to follow-up or had died. Patients who were admitted with chest pain, but had no manifestation of definite or possible AMI were also included in the analysis. Only p values <0.05 and 2-tailed t test were considered to have statistical significance. Student's t test, analysis of variance, and Z score test for proportions were used to obtain statistical significance.

TABLE I Characteristics of the Intervention and Control Groups at Entry to Study

Characteristic	Intervention Group (A)	Control Group (B)
No. of pts.	204	202
	Mean ± SD	
Age (yr)	50.5 ± 9.3	52.0 ± 8.3
Body mass index (wt/ht^2)	24.3 ± 1.1	23.3 ± 0.8
Blood pressure (mm Hg)		
Systolic	132.5 ± 5.4	134.2 ± 7.5
Diastolic	85.3 ± 2.6	88.4 ± 4.2
Cholesterol (mg/dl)		
Total	225.5 ± 46.2	228.5 ± 43.0
Low-density lipoprotein	170.2 ± 28.5	167.0 ± 25.1
High-density lipoprotein	44.5 ± 11.2	42.5 ± 9.9
Triglyceride (mg/dl)	172.2 ± 26.2	174.5 ± 28.0
Fasting blood sugar (mg/dl)	125.0 ± 10.5	122.5 ± 9.6
Blood urea (mg/dl)	24.2 ± 5.8	26.0 ± 5.5
Serum glutamic oxalacetic transaminase (IU)	140.5 ± 30.5	136.6 ± 26.8
Creatine phosphokinase (IU)	185.5 ± 48.6	178.6 ± 44.0
Site of AMI		
Inferior or posterior	36.7%	42.5%
Anterior and anteroseptal	34.3%	33.1%
Universal	28.9%	24.2%
Risk factors		
Male sex	88.2%	91.5%
Blood pressure (>150/95 mm Hg)	23.5%	21.7%
Smoker (≥1 cigarettes/day)	36.2%	34.6%
Serum cholesterolemia (>250 mg/dl)	25.5%	23.7%
Serum triglyceridemia (>190 mg/dl)	12.7%	14.8%
Diabetes mellitus (by G.T.T.)	17.1%	18.8%
Obesity (>10% of normal wt.)	28.4%	27.2%
Physical inactivity (<1 km/day walking)	57.8%	56.4%
Alcohol intake before AMI (>60 g/week)	22.0%	24.7%
Family history (by record)	9.8%	8.9%
History of coronary disease (by record)	17.6%	19.3%
Possible AMI	14.8%	17.8%
Unstable angina	4.9%	4.4%
Drug therapy		
Propranolol (40–240 mg/day)	46.5%	43.5%
Verapamil (20–60 mg/day)	24.5%	27.2%
Nitrates (60–180 mg/day)	98.0%	97.0%
Furosemide (20–80 mg/day)	14.1%	17.8%
Aspirin (175–355 mg/day)	90.6%	97.5%

AMI = acute myocardial infarction.

TABLE II Effect of Dietary Advice on Energy and Nutrient Intakes at Four Weeks in Patients Receiving Cardiovasoprotective and Typical Diets

Nutrient (daily)	Intervention Group A	Control Group B	p Value*
No. of pts.	204	202	
Total energy (Kcal, %/day)	1,432 ± 132	1,710 ± 150	<0.05
Energy intake per meal (carbohydrates, Kcal, %/day)	250 ± 45.5	456 ± 63.4	<0.05
Total	59.9 ± 0.72	56.6 ± 0.82	
Complex	51.0 ± 0.59	39.3 ± 0.53	<0.05
Refined	8.9 ± 0.18	17.3 ± 0.38	
Proteins			
Total	13.1 ± 0.33	15.4 ± 0.31	
Vegetable/fish	10.5 ± 0.29	6.4 ± 0.24	<0.05
Animal/milk	2.6 ± 0.18	9.0 ± 0.25	
Fatty acids			
Total	27.0 ± 0.44	28.0 ± 0.48	
Saturated	5.5 ± 0.24	10.2 ± 0.30	<0.01
Monounsaturated	10.0 ± 0.28	10.5 ± 0.28	
Polyunsaturated	11.5 ± 0.30	7.3 ± 0.26	<0.02
Polyunsaturated/saturated ratio	2.09 ± 30.0	0.71 ± 0.03	<0.02
Cholesterol (mg/day)	128.0 ± 30.0	266.5 ± 38.6	<0.02
Fiber (g/day)			
Total	41.8 ± 12.8	20.6 ± 9.6	<0.02
Cereal	10.2 ± 4.8	10.2 ± 4.0	
Vegetable/fruit	31.6 ± 8.2	10.4 ± 3.4	<0.02
Alcohol (g/week)	10.0 ± 6.0	28.3 ± 10.0	
Caffeine (mg/day)	28.5 ± 10.8	108.6 ± 18.8	<0.02
Salt (g/day)	3.6 ± 0.76	5.6 ± 0.85	<0.02
Vitamins and minerals (mg/day)			
Ascorbic acid	452.6 ± 106.6	188.6 ± 41.0	<0.02
Vitamin E	10.7 ± 2.5	8.6 ± 2.0	<0.05
Magnesium	1,070.0 ± 210.0	422.5 ± 112.0	<0.02
Potassium	3,050.0 ± 570.0	1,108.5 ± 221.0	<0.02
Copper	6.6 ± 0.71	2.3 ± 0.51	<0.02
Selenium (μg/day)	110.5 ± 30.6	75.6 ± 20.5	<0.02
Chromium (μg/day)	121.5 ± 24.5	85.5 ± 17.5	<0.02

Statistical significance by Student's t test.

TABLE III Changes in Laboratory Data Compared with Baseline in Intervention and Control Groups

	Intervention Group		Control Group		ANOVA F Value
	Baseline	Change	Baseline	Change	
No. of pts.	204	204	202	202	
Total cholesterol (mg/dl)	225.5 ± 46.2	−20.5	228.5 ± 43.0	−8.6	6.85 $p < 0.02$
Low-density lipoprotein cholesterol (mg/dl)	170.2 ± 28.5	−16.6	167.0 ± 25.1	−6.4	6.85 $p < 0.02$
High-density lipoprotein cholesterol (mg/dl)	44.5 ± 11.2	−1.5	42.5 ± 9.9	−1.3	1.23
Triglycerides (mg/dl)	172.2 ± 26.2	−15.5	174.5 ± 23.0	−7.6	7.82 $p < 0.02$
Fasting blood glucose (mg/dl)	125.0 ± 10.5	−14.8	122.5 ± 9.6	−6.8	5.82 $p < 0.02$
Blood urea (mg/dl)	24.2 ± 5.8	−1.5	26.0 ± 5.5	−2.1	1.12

p value obtained by application of ANOVA (F values) by comparison of changes in groups A and B.
ANOVA = analysis of variance.

RESULTS

During a period of 3 years, 505 patients with suspected AMI were considered for entry to this study, and 406 of these were randomly assigned to diet A (204) or B (202). The reasons for exclusion were: did not like dietary changes (12 patients), chronic disease such as cancer, diarrhoea, dysentery and blood urea >40 mg/dl (25 patients), death before randomization (20), and noncardiac pain (42).

Of the 406 patients that entered the trial, 204 received the cardiovasoprotective diet (group A) and 202 the prudent diet (group B) advised by doctors during AMI. At entry to the study, mean age, sex, mean body weight, blood pressure, lipoproteins, risk factors, complications, electrocardiographic changes, initial level of cardiac enzymes, and drug therapy were similar in both groups (Table I). All patients entered the trial within 24 to 48 hours of AMI. The diagnoses of definite and possible AMI, and ischemic heart disease were also comparable between the 2 groups. In both groups A (81%) and B (83%), the majority of patients left the hospital by the eleventh day.

The dietary intakes in all patients before AMI showed a similar daily intake of mean energy (2,110 vs 2,150 Kcal), total fat calories (26.0 vs 24.1%), polyunsaturated/saturated fat ratio (0.67 vs 0.65), dietary cholesterol (300 vs 310 mg), dietary fiber (27 vs 25 g) and salt (7.6 vs 8.2 g). Group A patients received a significantly higher percentage of calories from vegetable proteins, complex carbohydrates, polyunsaturated fat and fiber in the form of fruits, vegetables, nuts and fish. They also received decreased energy, cholesterol and saturated fatty acids compared with those of group B (Table II).

Withdrawal: Of 406 patients initially randomized, 5 in group A, and 4 in group B were lost during 6-week follow-up. Of the remaining patients, 45 in group A, and 52 in group B were lost after discharge from the hospital, but later rejoined the same group. Withdrawals from group A had substantial decreases in blood lipids, indicating that they were following the dietary advice. Side effects of the group A diet were mild belching and fullness.

Blood lipids and glucose: Whereas pretrial lipid levels showed no significant difference, after 6 weeks there was a significant decrease in mean serum and low-density lipoprotein cholesterols, triglycerides and blood glucose, and a nonsignificant decrease in high-density lipoprotein cholesterol in group A compared with those in group B (Table III). In both groups, most patients (80.2%) had serum cholesterol levels between 200 and 260 mg/dl.

Body weight and blood lipids: Initial body weight in the intervention (66.6 ± 10.5 kg, range 52 to 84) and control (65.3 ± 8.8 kg, range 52 to 83) groups at entry to the study was similar. However, after 6 weeks of therapy with 2 dietary regimens, both groups A (63.2 ± 8.7 kg, range 52 to 78) and B (64.0 ± 10.3 kg, range 52 to 80) showed a decrease in mean body weight (3.4 and 1.3 kg, respectively). Patients with obesity showed no significant decrease from baseline to after 6 weeks in groups A (58 vs 46) and B (55 vs 50). In group A, 97 patients lost >0.5 kg of body weight, whereas in group B, only 23 patients lost >0.5 kg. A separate analysis of data in the 97 patients within group A with weight reduction showed a more significant decrease in serum (197.2 ± 19.2 mg/dl, range 145 to 280) and low-density lipoprotein (147.2 ± 25.2 mg/dl, range 95 to 210) cholesterols, and triglycerides (144.3 ± 10.5 mg/dl, range 95 to 215), with a nonsignificant increase in high-density lipoprotein cholesterol (45.5 ± 10.0 mg/dl, range 38 to 62), without such changes in serum total (210.5 ± 21.5 mg/dl, range 145 to 295) and low-density lipoprotein (158.2 ± 27.8 mg/dl, range 92 to 220) cholesterols, triglycerides (161.3 ± 20.4 mg/dl, range 96 to 226) and high-density lipoprotein cholesterol (42.0 ± 9.4 mg/dl, range 35 to 60) in the remaining 107 patients of group A.

Smoking: Smoking was completely stopped in both groups during hospitalization. However, after discharge from the hospital, 18 of 74 smokers in group A, and 12 of 70 in group B began smoking again (3 to 8 cigarettes/day) during 6-week follow-up.

Complications and cardiac end points: Complications such as angina pectoris, electrocardiographic changes after exercise, left ventricular hypertrophy, ven-

TABLE IV Complications and Cardiac End Points in Intervention and Control Groups After Six Weeks of Acute Myocardial Infarction

	Intervention Group A (%)	p Value	Control Group B (%)	Difference (%)
No. of pts.	204		202	
Complications				
Angina pectoris	8 (3.9)	p <0.02*	35 (17.3)	77.4
Positive exercise electrocardiogram	102 (50.0)	p <0.02*	165 (81.6)	38.7
Left ventricular strain	8 (3.8)		22 (10.9)	64.2
Left ventricular hypertrophy	15 (7.8)		21 (10.4)	25.0
NYHA class III and IV heart failure	6 (2.9)		12 (5.9)	50.8
Ventricular ectopics (>8/min)	16 (7.8)	p <0.02*	35 (17.3)	54.9
Ventricular ectopics (>3 consecutively)	4 (1.9)		15 (7.4)	74.3
Total complications	160 (78.4)	p <0.001*	305 (150.9)	48.0
Cardiovascular end points				
Nonfatal myocardial infarction	17 (8.3)		25 (12.3)	32.5
Fatal myocardial infarction	8 (3.9)		12 (5.9)	33.8
Sudden cardiac death (<1 hour)	4 (1.9)		7 (4.2)	54.7
Suspected cardiac death	—		1 (0.4)	—
Total cardiac mortality	12 (5.8)		20 (9.9)	41.4
Total mortality	12 (5.8)		21 (10.4)	42.2
Total cardiac end points	29 (14.2)	p <0.01*	44 (21.7)	34.5
Total cardiovascular events	29 (14.2)	p <0.01*	45 (22.2)	36.0

*p value; significance obtained by test for proportions (Z test), 2-tailed.
Effectiveness = control % − intervention % × 100/control %.
NYHA = New York Heart Association.

tricular ectopics (>8/min) and total complications were significantly decreased in group A compared with those in group B after 6-week follow-up (Table IV).

Total cardiac end points including nonfatal (17 vs 25) and fatal (8 vs 12) AMI, and sudden cardiac death (4 vs 7) were significantly (29 vs 44, p <0.01) decreased (34.5%) in group A compared with those in group B. Total cardiac mortality (12 vs 20) and total mortality (12 vs 21) showed no significant difference owing to the small number of events (Table IV).

Weight reduction, complications and cardiac end points: In group A, 97 patients lost >0.5 kg of body weight, whereas 107 did not. After 2-week follow-up, deaths in these 2 subsets of patients were equal (2 vs 3). The incidences of complications in the remaining 95 patients with and 104 without weight loss during the last 4 weeks of the trial were: angina pectoris: 1.0 vs 6.7%; positive exercise electrocardiogram: 23.1 vs 72.1% (p <0.01); left ventricular strain: 1.0 vs 4.8%; and left ventricular hypertrophy: 3.1 vs 9.6%; New York Heart Association class III and IV heart failure: 1.0 vs 1.9%; ventricular ectopics (8/min): 5.2 vs 9.6%; and total complications: 34.7 vs 104.8% (p <0.01).

Total cardiac end points after 2 weeks in these 2 subsets of the intervention group, including nonfatal (7 vs 10) and fatal (3 vs 2) AMI, and sudden cardiac death (0 vs 2), showed no significant (10 vs 14) decrease (22.0%) in relation to weight reduction, which may be owing to the small number of cases, and only 6-week follow-up.

DISCUSSION

Most deaths due to AMI occur soon after the onset of its manifestations; therefore, it is necessary to initiate any potentially useful treatment immediately after it is suspected.[1,2] Because the treatment under scrutiny may be harmful rather than beneficial to patients without AMI, all those (irrespective of subsequent changes in diagnosis or withdrawal from the trial) must be followed up, and overall benefit or harm must be assessed in each intention to treat group, whether they have possible AMI or unstable angina without AMI. This study showed that comprehensive dietary changes in association with weight loss during 6-week follow-up 48 to 72 hours after AMI were associated with significant decreases in total and low-density lipoprotein cholesterols, triglycerides and fasting blood glucose, with an insignificant decrease in high-density lipoprotein cholesterol compared with the initial levels and changes in group B patients (Table III). These changes in lipoproteins in group A and B patients were associated with a significant decrease (34.5%) in total cardiac end points in group A (29 vs 44, p <0.01) compared with those in group B. The decreases in total number and rate of nonfatal AMI was nonsignificant (17 vs 25) compared with those in group B. The differences in total and cardiac mortality were insignificant owing to the small number of events (Table IV). The size of the study group was small, and the time of observation was only 6 weeks; hence, it is not possible to draw more definite conclusions. The highest number of cardiac end points (includ-

ing mortality) was in patients with angina, arrhythmias and extensive AMI. These findings are similar to those of other studies.[1,2] The cardiac mortality (5.8 vs 9.9%) and end-point rate (14.2 vs 21.7%) in groups A and B were lower than those (10 to 15%) during the first few weeks of AMI in other studies, because interventions were performed in both groups.[1,2] The differences in mortality could be due to the absence of intervention in the control group; hence, these changes in mortality may be of significant value.

We believe that the present study is the first controlled trial of a low-energy fat-modified diet rich in fruits, vegetables and nuts administered as treatment within 72 hours of AMI. Compliance was fairly good, and there was some tendency to consume a low-energy intervention diet in the control group not given this treatment. In 1 recent controlled and randomized study comprising 2,033 patients,[9] an increased intake of fish was associated with a 29% reduction in 2-year all-cause mortality. In other randomized trials,[6,8,25] a fat modified diet or one with a high polyunsaturated/saturated fat ratio was administered to subjects who had recovered from AMI. All these trials comprised <500 subjects, and a nonsignificant decrease in mortality was reported.

In most dietary trials, the issue of compliance is a problem, because subjects in the intervention group may not eat exactly what they are advised to. However, in AMI patients, seriousness of illness tends to motivate them to eat what they are advised by the dietitian. The diets were supervised during the first 10 days of AMI; however, in the later period compliance was primarily monitored by questionnaire, which is open to bias because subjects may give the wrong answer to questions asked by the dietitian. The next important problem in dietary trials is blinding. The attending physician kept a detailed record of complications and end points in all patients; however, the final diagnosis was performed by another physician unaware of the dietary regimens who obtained diagnoses based on examination of the records of these patients on earlier described criteria[21] without having access to the patients. Furthermore, the attending physician always declined to give dietary advice.

Group A patients received a fat-modified low-caloric diet rich in polyunsaturated fatty acids, water-soluble dietary fiber, vitamins and minerals compared with that of group B, which received higher saturated fat and cholesterol (Table II). Minerals and vitamins in the diet are known to decrease free radical generation and prevent the decrease in high-density lipoprotein cholesterol, and inhibit thrombosis (although of controversial value).[10-12,26] A low-energy and low-fat, high-polyunsaturated fat diet is known to modulate not only blood lipids and thrombosis,[4] but also the secretion of catecholamines, and blood pressure, and to have a beneficial influence on cardiac indexes.[27,28]

Apart from qualitative changes in the diet, group A patients also received significantly lower total calories than did group B, resulting in significantly greater reduction in body weight in group A (3.4 vs 1.3 kg). Both qualitative changes in the diet (Table III) and weight loss in group A were associated with better modulation of lipoproteins and blood glucose than in group B. Group A patients who also had a weight loss >0.5 kg (97 patients) had a greater decrease in blood lipids, without a decrease in high-density lipoprotein cholesterol. Although total cardiac end points showed no significant difference owing to the small number of group A patients with and without weight loss, total complications were 66.8% less among those with weight reduction than those without (34.7 vs 104.8%, <0.01). There is evidence that a low-energy diet can modulate blood lipids,[29] and that reduction of body weight in patients with enlarged hearts[30] decreases cardiac size and may reduce left ventricular strain and electrocardiographic changes after exercise. In conclusion, the Indian experiment demonstrates for the first time that a low-energy diet characterized by small frequent meals rich in fruits, vegetables, nuts and cereals can cause significant decreases in cardiac end points in patients within the first 6 weeks of AMI. A multicenter trial in a large number of patients and a longer follow-up may be necessary to confirm our observations.

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Early Hemodynamic Results of Left Ventricular Reconstructive Surgery for Anterior Wall Left Ventricular Aneurysm

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To assess the efficacy of left ventricular (LV) reconstruction after aneurysmectomy, 35 consecutive patients with anterior LV aneurysm were studied before and after surgery. Surgical technique was performed by applying a circular patch after aneurysmectomy to maintain a "more physiological" LV cavity. Myocardial revascularization was performed in all but 1 patient concurrently. Global perioperative mortality was 4.8%. LV filling pressure and volumes and regional wall motion were assessed before and after surgery. The major indication for surgery was angina; 8 patients were in New York Heart Association class III/IV.

The results showed a significant decrease in end-diastolic volume index (from 120 ± 55 ml/m² to 76 ± 22 ml/m², p <0.001), end-systolic volume index (from 74 ± 44 ml/m² to 40 ± 18 ml/m², p <0.001) and end-diastolic pressure (from 17 ± 7 mm Hg to 13 ± 5 mm Hg, p <0.05). Ejection fraction significantly increased (from 39 ± 13% to 49 ± 15%, p <0.001). LV wall motion significantly improved in all but the anterobasal region; the extent of LV asynergy significantly decreased after surgery. Six of the 35 patients had a deterioration of postintervention ejection fraction (from 44 ± 14% to 34 ± 9%). They had no reduction in LV volumes and no improvement in wall kinetics.

It is concluded that LV reconstruction after aneurysmectomy induces significant early improvement of global and regional LV function in most patients; postoperative functional improvement is mainly related to the increase in inferior LV wall motion.

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The efficacy of standard surgical repair for left ventricular (LV) aneurysm remains uncertain.[1,2] Although many studies reported improved symptoms after aneurysmectomy, most failed to demonstrate a concurrent improvement in global LV function.[3–7] Standard linear repair of LV aneurysm may bring about a distortion of LV chamber even greater than that which existed before surgery.[8,9] Therefore, new techniques for geometric reconstruction after aneurysmectomy have been proposed.[9–11]

Early and late results (on surgical outcome with regard to LV function) exploring the efficacy of such new operative techniques in a consecutive series of patients are scarce.[9,10] The present series include all patients referred to the Monaco Cardiothoracic Center for anterior LV aneurysm between June 1988 and October 1989. All patients were treated with LV reconstruction after aneurysm resection and had cardiac catheterization, LV angiography and coronary arteriography before and after surgery.

METHODS

Patients: The series included all patients with previous anterior wall myocardial infarction lasting longer than 1 month, evaluated at the Monaco Cardiothoracic Center from June 1988 to October 1989, whose ventricular angiograms indicated a potentially resectable LV aneurysm and who underwent reconstructive surgical repair. Patients with previous posterior myocardial infarction or with angiographic posterior aneurysm, or both, were excluded.

There were 44 patients with anterior LV aneurysm as defined by the Coronary Artery Surgery Study angiographic criteria.[12] Diagnosis was confirmed at surgery in all but 3 patients who were excluded from the study group. In the perioperative period there were 2 deaths, a 4.8% operative mortality rate. Four patients were excluded because they refused control hemodynamic study. In all, 35 patients (2 women and 33 men, mean age 55 ± 9 years) represent the present series.

Thirty-four of the 35 patients had complete myocardial revascularization concurrently. Internal mammary artery was implanted on the left anterior descending artery in 30 patients, and on the first diagonal branch in 4. Saphenous vein grafts were applied on the other vessels when indicated. Patients gave informed consent for the control hemodynamic study which was performed 15 days after surgery.

Diagnostic procedure before and after surgery: All patients underwent left-sided cardiac catheterization

TABLE I Mean Hemodynamic Data and Regional Left Ventricular Wall Motion Before and After Surgery (n = 35)

	EDP	EDVI	ESVI	EF	AB	AL	AP	DI	PB	A%
PRE	17	120	74	39	−1.3	−2.4	−3.1	−1.5	−0.3	42
SD	7	55	44	13	1.1	0.6	0.5	1.0	1.7	17
	*	†	†	†	NS	*	†	†	*	†
POST	13	75	40	49	−1.1	−1.9	−2.1	−0.1	0.8	29
SD	5	22	18	15	1.1	.9	1.1	1.7	2.1	20

*$p < 0.05$; †$p < 0.001$.
A% = extent of left ventricular asynergy (%); AB = anterobasal region (mean Z value); AL = anterolateral region (mean Z value); AP = apical region (mean Z value); DI = diaphragmatic region (mean Z value); EDP = end-diastolic pressure (mm Hg); EDVI = end-diastolic volume index (ml/m^2); EF = left ventricular ejection fraction (%); ESVI = end-systolic volume index (ml/m^2); NS = not significant; PB = posterobasal region (mean Z value); POST = postintervention data; PRE = preintervention data.

through the right femoral artery. LV angiography was performed in right anterior oblique 30° projection (50 frames/s) with an Angioskope Siemens equipment using a nonionic contrast medium. Coronary arteriography was performed using the Judkins technique.

The extent of coronary artery disease was estimated by applying the Gensini score.[13] All patients had at least a critical stenosis on the left anterior descending artery (>75%).

End-diastolic and end-systolic LV outlines were manually traced and volumes were computed with the Chapman monoplane method.[14] Total ejection fraction was calculated as: (end-diastolic volume − end-systolic)/end-diastolic volumes.

Residual contractile segment ejection fraction was calculated by applying the single-plane method described by Kapelanski et al.[15]

Left ventricular wall motion analysis: Regional wall motion was analyzed with the centerline method.[16] Systolic shortening fraction of 90 chords, from the aortic (chord 1) to the mitral corner (chord 90), was calculated. The values observed in the study group were compared with those obtained in a group of 16 normal subjects by calculating a "Z" value for each chord; systolic shortening fraction was converted into units of normal standard deviation from the mean systolic shortening fraction of the normal group and calculated as: Z = (systolic shortening fraction − mean systolic shortening fraction of the normal group)/standard deviation of the normal group.

Finally, regional wall motion was assessed by calculating the average Z from the individual Z values of the chords pertaining to different regions identified by subdividing the LV contour into 5 sectors: anterobasal, anterolateral, apical, diaphragmatic and posterobasal.

The percent length of the perimeter showing Z value >2 SD from the normal mean was taken as an index of the extent of the asynergy.

Mean shortening fraction of the remaining chords within the LV perimeter was taken as an index of shortening of the residual contractile myocardium and expressed as Z value.

Operative technique: Surgical technique has been described in detail in previous studies.[10,17] Briefly, it involved an endoventricular circular patch plasty with septal exclusion, using a circular patch of synthetic or autologous tissue anchored inside the left ventricle in the contractile myocardium, after the resection or exclusion of the aneurysm. Thus, a more physiologic LV cavity is maintained and the restraint caused by the linear suture closure is avoided. Myocardial revascularization is performed when indicated.

Statistical analysis: Hemodynamic results were evaluated by applying the paired or unpaired *t* test. Surgical outcome and preoperative data have been evaluated with multivariate analysis.

RESULTS

Venous grafts and internal mammary arteries were all patent and well-functioning at control. Table I lists mean hemodynamic data and regional LV wall motion before and after surgery in the whole group of patients. End-diastolic volume index, end-systolic volume index and end-diastolic pressure significantly decreased. Ejection fraction significantly increased. Systemic pressure and cardiac output did not change significantly after surgery. Regional wall kinetics significantly improved after operation except in anterobasal region. The index of the extent of asynergy significantly decreased after operation. Figure 1 shows mean shortening fraction before and after intervention in the total group of patients, expressed as absolute and as Z values from normal mean. Postintervention values were significantly improved in apical and inferior wall.

Within the group there were 6 patients who had a decrease in ejection fraction after aneurysmectomy (from 44 ± 14% to 34 ± 9%) (group I) and 29 patients who had an increase (from 37 ± 13% to 52 ± 14%) (group II). No significant differences were found in hemodynamic and wall motion parameters before intervention. No relation was found between ejection fraction and the site of stenosis on the left anterior descending artery (proximal or distal) after intervention. Table II lists mean values in the 2 groups of patients before and after intervention.

In group I end-diastolic and end-systolic volume indexes did not change significantly, whereas end-diastolic pressure significantly decreased. These patients did not have significant improvement in regional wall kinetics, and had a significant decrease in wall motion in the anterobasal region; the index of the extent of asynergy did not change significantly after surgery.

Patients in group II had a significant decrease in end-diastolic and end-systolic volume indexes and end-diastolic pressure. Regional wall motion significantly improved in anterolateral, apical, diaphragmatic and

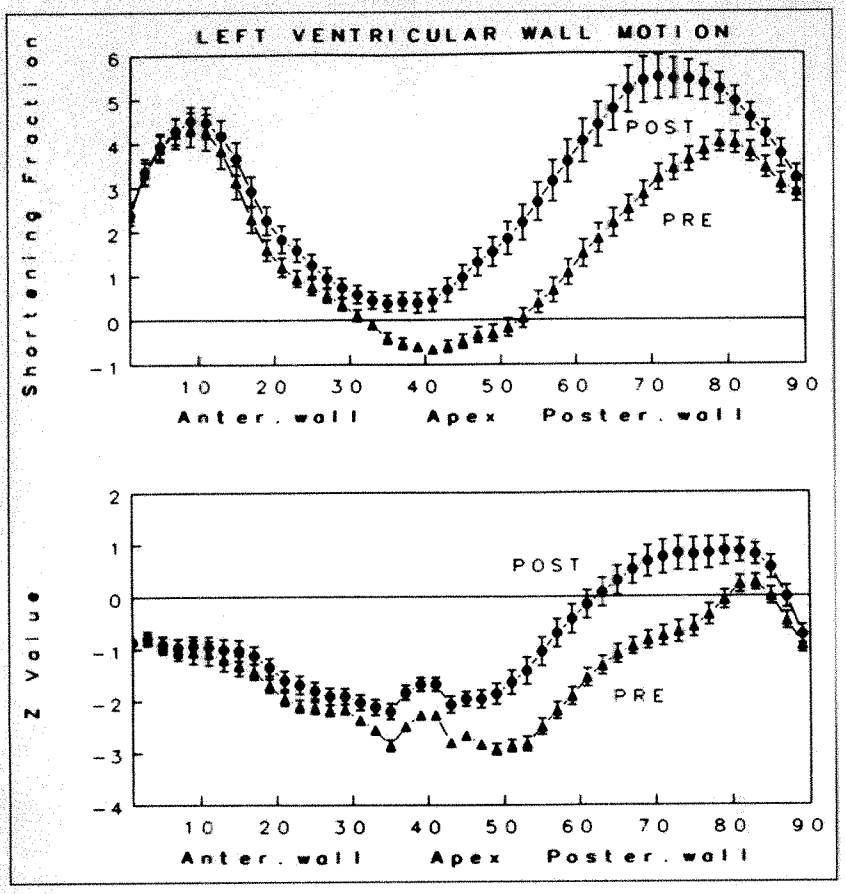


FIGURE 1. Pre- and postoperative shortening fraction in the entire group of patients (n = 35). *Top,* absolute values; *bottom,* standard deviation from the normal mean values (Z value). Anter. = anterior; Poster. = posterior.

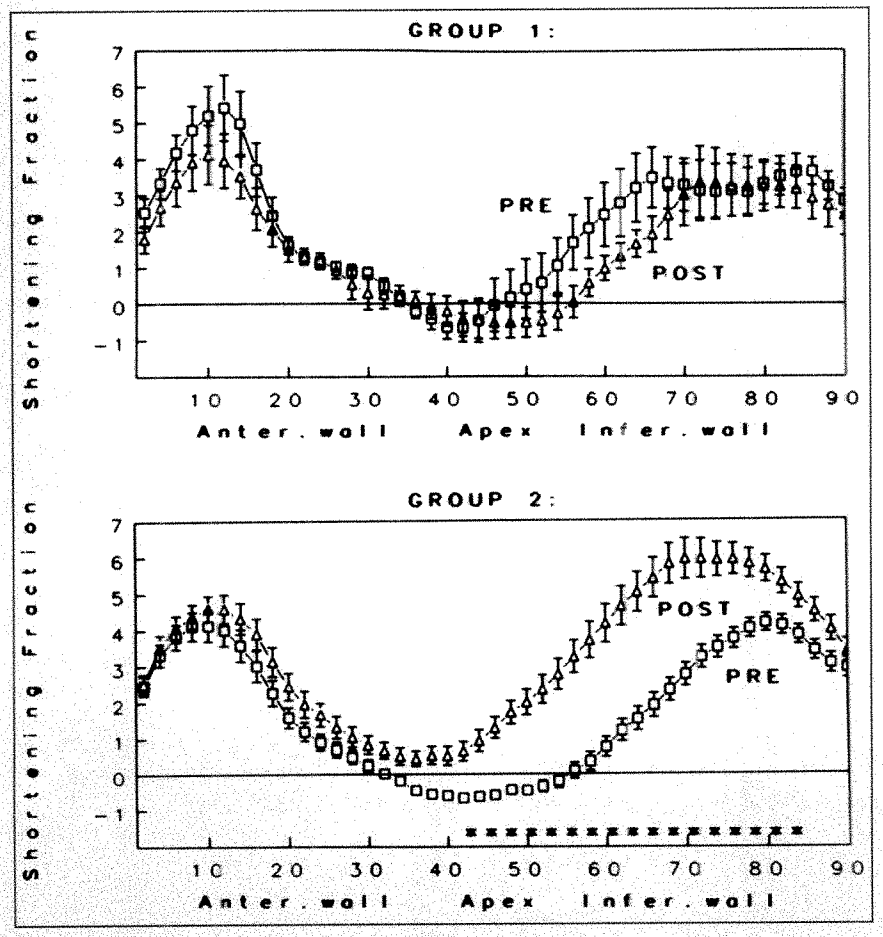


FIGURE 2. Absolute values of pre- and postoperative shortening fraction in 2 groups of patients: group patients with postoperative deterio ration in global ejection fraction; group II, patients with postoperative improvement in global ejection fraction. *p <0.05. Abbreviations as in Figure 1.

TABLE II Mean Values Before and After Intervention

	Group I (n = 6)			Group II (n = 29)		
	Pre	Post		Pre	Post	
EDVI	98 ± 29	74 ± 27	NS	124 ± 58	76 ± 22	†
ESVI	57 ± 28	50 ± 24	NS	79 ± 46	38 ± 17	†
EDP	18 ± 5	12 ± 4	*	16 ± 8	14 ± 6	*
AB	−0.8 ± 0.95	−1.5 ± 0.98	*	−1.4 ± 1.1	−1.0 ± 1.18	NS
AL	−2.3 ± 0.24	−2.3 ± 0.60	NS	−2.5 ± 0.63	−1.8 ± .94	†
AP	−2.7 ± 1.06	−3.1 ± 0.77	NS	−3.1 ± 0.31	−1.9 ± 1.00	†
				*		
DI	−0.8 ± 1.40	−1.7 ± 0.76	NS	−1.6 ± 0.88	0.3 ± 1.76	†
				**		
PB	−0.6 ± 1.57	−1.2 ± 1.78	NS	−0.2 ± 1.74	1.1 ± 1.97	†
				*		
A%	32 ± 18	44 ± 15	NS	43 ± 16	26 ± 20	†
CSEF	51 ± 12	—		46 ± 11	—	
CSF	−0.7 ± 0.6	—		−0.7 ± 0.5	—	
Gensini score	85 ± 16	—		72 ± 30	—	
n Bypass	—	2.3 ± 0.5		—	1.9 ± 0.9	

*$p < 0.05$; †$p < 0.001$.
CSEF = contractile segment ejection fraction (%); CSF = contractile shortening fraction (expressed as mean Z value); other abbreviations as in Table I.

posterobasal regions, whereas it did not change in the anterobasal region. The index of the extent of asynergy was significantly reduced.

Figure 2 shows mean values of systolic shortening fraction expressed as absolute values before and after surgery in the 2 groups of patients. After intervention, values of regional wall motion were significantly different in the 2 groups for apical, diaphragmatic and posterobasal regions (Table II).

DISCUSSION

Studies assessing LV function after aneurysmectomy have given conflicting results: Some showed improvement after operation,[4,18,19] while others did not.[3,5,7,20,21] Furthermore, many studies relating to the efficacy of surgery for LV aneurysmectomy do not provide detailed postoperative evaluation of patients, and most of them refer to standard linear repair of the aneurysm.

In this respect our series is unique in that patients were consecutive, underwent LV reconstructive surgery after aneurysmectomy and had hemodynamic and angiographic evaluation before and after operation.

Our results indicate that the operative technique of LV reconstruction after aneurysmectomy can be performed with a low surgical risk. Global mortality rate was 4.8% in our series. Previous studies have reported a surgical risk for LV aneurysmectomy ranging between 9 and 21%, with the highest mortality in patients with congestive heart failure.[22-30] In our series, angina and not congestive heart failure dominated the clinical picture.

A significant early improvement in global and regional LV function was obtained in most of our patients (83%). Hemodynamic parameters were also favorably affected by LV reconstruction in that LV filling pressure decreased in all patients and LV volumes decreased in most. These changes strongly suggest an increased LV compliance, and may be interpreted on the basis of the conceptual model proposed by Swan et al,[27] which was verified in a clinical series by Feild et al.[28] According to this model, aneurysm resection may increase LV compliance by excluding the scarred, rigid tissue and saving the more compliant, contractile myocardium. If the LV wall were uniformly noncompliant, a surgically induced great reduction in chamber size would lead to an increase in diastolic pressure, according to Laplace's law. The same mechanism can be responsible for the significant decrease in end-diastolic pressure in group I patients whose LV volumes did not change and whose LV pump function deteriorated after intervention.

Many attempts have been made to find prognostic indexes that relate to operative survival and functional improvement. Most of the workers agree that residual segment ejection fraction, i.e., the contractility of the nonaneurysmal segments, is an important predictor of the results of aneurysmectomy. Global ejection fraction, LV volumes and filling pressure have not been found useful in this respect. However, in the Coronary Artery Surgery Study neither LV score nor residual LV score (an index of the function of the nonaneurysmal portion of the left ventricle) related to the surgical outcome.[1,2] In our series, the residual contraction of the nonaneurysmal portion of the left ventricle did not show significant differences between patients who were well after operation and patients who were not.

According to Froelich et al,[3] the lack of improvement in LV function can be related to the fact that a substantial portion of the involved area is not resected, but this is not the case in our series.

Other investigators[24] have found that dyskinetic aneurysms have a more favorable surgical outcome than akinetic aneurysms. In our patients no significant differences were found in the preoperative extent and type of asynergy.

Our data indicate that a favorable surgical outcome (in terms of improved ejection fraction) appears to be related to a greater increase in inferior wall systolic

shortening. This result may be influenced by surgical revascularization of the left circumflex or the right coronary artery; however, no differences in either the coronary lesions or in the number of bypassed vessels were found among patients who had an increase or a decrease in ejection fraction after surgery. Therefore, our results and the lack of benefit that has been reported in other studies exploring the effects of LV aneurysmectomy combined with revascularization strongly support the hypothesis that improvement in LV function has to be related to a more favorable LV geometry obtained with this operative technique and not only to myocardial reperfusion.

The longitudinal section used for the standard repair of LV aneurysm can induce a marked alteration of fiber architecture, thus leading to an impairment in the contraction recovery of asynergic ischemic segments and, in turn, to a depression in global LV function. Geometric LV reconstruction can, instead, allow a good recovery of contraction in the reperfused zones with a consequent improvement in global function.

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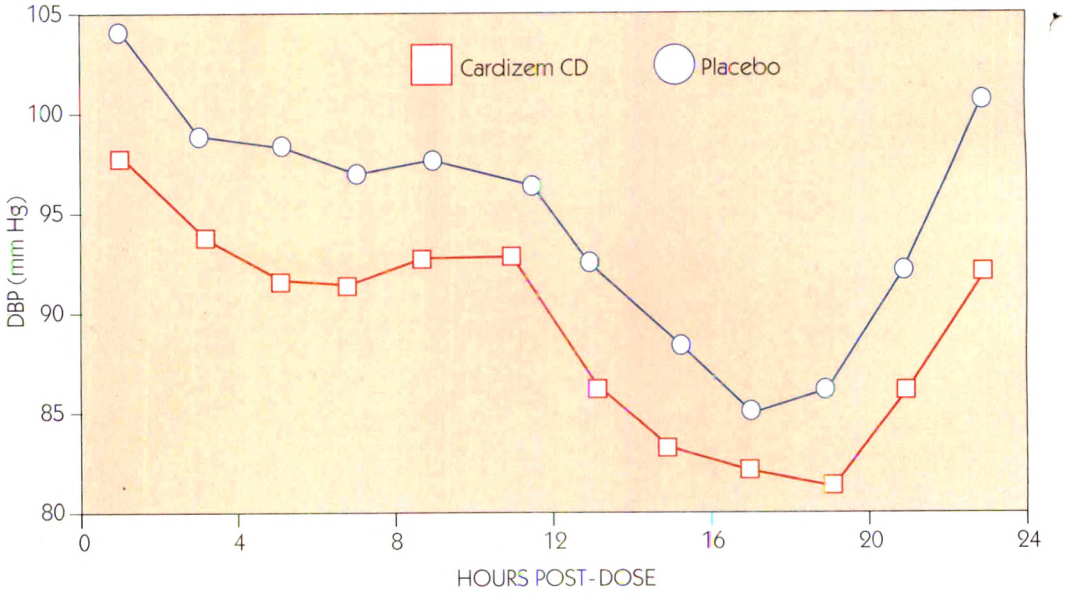
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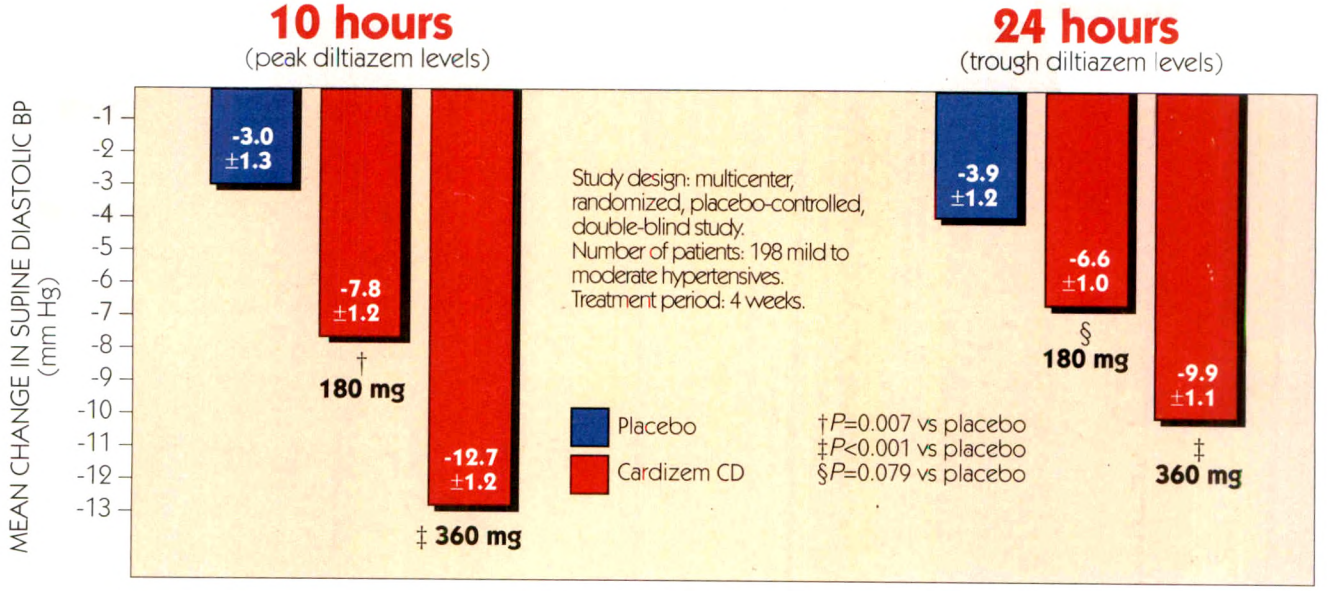
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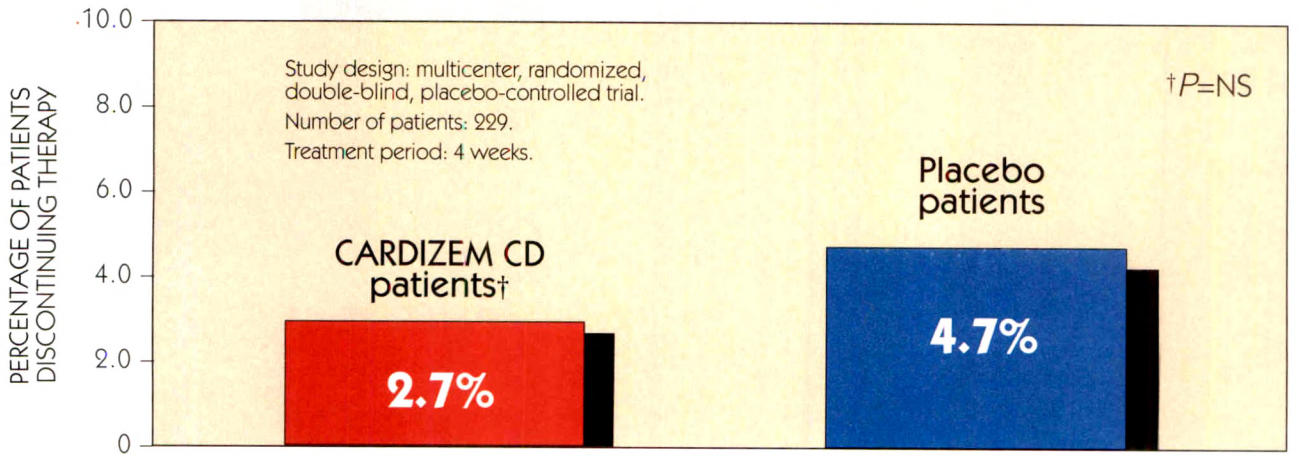
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A FAVORABLE HEMODYNAMIC PROFILE

Decreases peripheral vascular resistance, and does not compromise cardiac output[4]*†

Does not compromise renal blood flow and glomerular filtration rate and decreases renal vascular resistance[4-7]†

Increases coronary blood flow[1,3]

* As seen in patients with normal LV function. Caution should be used in patients with congestive heart failure.

† As seen in studies lasting up to 12 months. The effects of diltiazem on these renal and cardiovascular parameters past 12 months are unknown.

NEW

RARELY CAUSES ADVERSE METABOLIC EFFECTS

No significant changes in total cholesterol and triglycerides[1]

Rarely causes adverse effects on glucose or electrolytes[1,2,8‡]

DOSING INFORMATION

Available as 180-, 240-, and 300-mg dosage strengths

Once-A-Day



180-mg capsules



240-mg capsules



300-mg capsules

For new patients starting on Cardizem CD:

- Start with one 180-mg capsule daily
- Monitor for 2 weeks; if optimal response is not met
- Titrate to goal blood pressure

For patients switching from Cardizem SR:

- Switch on a total mg/day basis
- If necessary, titrate to goal blood pressure

NEW

ONCE-A-DAY

CARDIZEM® CD

(diltiazem HCl)

ONE TO TRUST FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

‡ The incidence of hyperglycemia reported with diltiazem has been <1%.

Please see brief summary of prescribing information on next page.

20021A2

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONCE A DAY

ONE TO TRUST

FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.



ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=394	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%) flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg and 120 mg in bottles of 100, and in UDIP® packages of 100.

Product Information as of October 1991

References: **1.** Data on file, Marion Merrell Dow Inc. **2.** Andrén L, Hedgund P, Dotevall A, et al. *Am J Cardiol.* 1988;62:114G-120G. **3.** O'Rourke RA. *Am J Cardiol.* 1985;56:34H-40H. **4.** Amodeo C, Kobrin I, Ventura HO, Messerli FH, Frohlich ED. *Circulation.* 1986;73(1):108-113. **5.** Demarie BK, Bakris GL. *Ann Intern Med.* 1990;113(12):987-988. **6.** Sunderrajan S, Reams G, Bauer JH. *Am Heart J.* 1987;114:383-388. **7.** Isshiki T, Amodeo C, Messerli FH, Pegram BL, Frohlich ED. *Cardiovascular Drugs and Therapy.* 1987;1:359-366. **8.** Frishman WH, Zawada ET Jr, Smith LK, et al. *Am J Cardiol.* 1987;59:615-623.

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PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

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Correlations Among Time and Frequency Domain Measures of Heart Period Variability Two Weeks After Acute Myocardial Infarction

J. Thomas Bigger, Jr., MD, Joseph L. Fleiss, PhD, Richard C. Steinman, AB, Linda M. Rolnitzky, MS, Robert E. Kleiger, MD, and Jeffrey N. Rottman, MD

Seven hundred fifteen participants from a multicenter natural history study of acute myocardial infarction were studied (1) to determine the correlations among time and frequency domain measures of heart period variability, (2) to determine the correlations between the measures of heart period variability and previously established postinfarction risk predictors, and (3) to determine the predictive value of time domain measures of heart period variability for death during follow-up after acute myocardial infarction. Twenty-four hour electrocardiographic recordings obtained 11 ± 3 days after acute myocardial infarction were analyzed and 11 measures of heart period variability were computed. Each of 4 bands in the heart period power spectrum had 1 or 2 corresponding variables in the time domain that correlated with it so strongly ($r \geq 0.90$) that the variables were essentially equivalent: ultra low frequency power with SDNN* and SDANN index,* very low frequency power and low-frequency power with SDNN index,* and high-frequency power with r-MSSD* and pNN50.* As expected from theoretical considerations, SDNN and the square root of total power were almost perfectly correlated. Correlations between the time and frequency domain measures of heart period variability and previously identified postinfarction risk predictors, e.g., left ventricular ejection fraction and ventricular arrhythmias, are remarkably weak. Time domain measures of heart period variability, especially those that measure ultra low or low-frequency power, are strongly and independently associated with death during follow-up.

*** Defined in Table II.**

(Am J Cardiol 1992;69:891–898)

From the Division of Cardiology, Department of Medicine, and Division of Biostatistics, School of Public Health, Columbia University; and the Division of Cardiology, Department of Medicine, The Jewish Hospital of St. Louis, Washington University School of Medicine, St. Louis, Missouri. This study was supported in part by Grants HL-41552 and HL-70204 from the National Heart, Lung, and Blood Institute, and Grant RR-00645 from the Research Resources Administration, National Institutes of Health, Bethesda, Maryland; and by funds from The Milstein Family Foundation, The Dover Foundation, George and Abby O'Neill, Robert Winthrop, and the Shirlee and Henry Benach Foundation, New York, New York. Manuscript received October 25, 1991; revised manuscript received and accepted December 2, 1991.

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In 1987, we showed that the standard deviation of normal RR intervals over 24 hours (SDNN) predicts all-cause mortality after myocardial infarction independently of the major risk factors identified by the Multicenter Post Infarction Program (MPIP), i.e., New York Heart Association functional class, pulmonary rales in the coronary care unit phase of the infarction, radionuclide left ventricular ejection fraction, and the frequency of ventricular arrhythmias.[1] However, SDNN measures all sources of heart period variability and thus provides little insight into the physiologic mechanisms causing risk. Power spectral analysis of heart period variability has been used to evaluate the autonomic nervous system in normal human subjects[2,3] and in patients after myocardial infarction.[4] In 1992, we reported that several frequency domain (power spectral) measures of heart period variability are also significantly associated with death during follow-up after myocardial infarction.[5] Other time domain measures of heart period variability have been suggested as predictors of mortality, but have not been evaluated in a large patient group.[6] The purposes of this study were (1) to determine the correlations among time and frequency domain measures of heart period variability, (2) to determine the correlations between the measures of heart period variability and previously established postinfarction risk predictors, and (3) to determine the predictive value of time domain measures of heart period variability for death during follow-up after myocardial infarction.

METHODS

Study design: To measure heart period variability after myocardial infarction, we reanalyzed the 24-hour continuous electrocardiographic recordings from the MPIP, a longitudinal study that enrolled 867 patients from diverse geographies and categories of hospitals.[7] Left ventricular function, arrhythmia and myocardial ischemia were assessed 2 weeks after myocardial infarction and related to mortality during 2 to 4 years of follow-up. These features make the results of MPIP widely generalizable to the general population of patients with recent myocardial infarction in the United States. The details of enrollment, measurement of baseline variables, quality control procedures, and follow-up for MPIP have been described previously.[7,8]

Processing of 24-hour Holter tapes: The 24-hour electrocardiographic recordings were reprocessed for heart period variability using recently described methods.[9–11] Briefly, 24-hour recordings were A/D converted on a Marquette 8000 scanner at 128 samples per sec-

TABLE I Reasons Tapes Were Excluded from the Study

Tape not recorded	47
Tape deteriorated in storage	36
Insufficient data*	48
Atrial fibrillation	7
Other rhythm disturbance	14

*To qualify, a tape was required to have 12 hours or more of analyzable data with ≥2.5 hours of analyzable data during the nighttime period (50%) and ≥7.0 hours of analyzable data during the daytime period (50%). At least half the data had to be sinus rhythm during the nighttime period, during the daytime period, and overall.

ond. Initial QRS labeling and editing were done with the standard Marquette algorithms (version 5.7 software). Then, the data files were transferred via high speed link from the Marquette scanner to a Sun workstation where, using algorithms developed at Columbia University, a second stage of editing was done to find and correct errors that could adversely affect measurement of heart period variability.[12] For a tape to be eligible for this study we required that it have ≥12 hours of analyzable data and have at least half of the nighttime and half of the daytime periods analyzable. Also, at least half of the daytime, half of the nighttime and half of the data overall had to be sinus rhythm. Tapes from 152 patients were not analyzed for heart period variability for the reasons listed in Table I.

Frequency domain analysis of normal RR intervals: After the second stage of editing and review of the results by a cardiologist, the heart period power spectrum was computed over a 24-hour interval using a method first described by Albrecht and Cohen[10] and adapted by Rottman et al.[11] First, a regularly spaced time series was derived from the RR intervals by sampling the irregularly spaced series defined by the succession of normal RR intervals in each 24-hour recording. For each time series 2^{18} points were sampled at equal intervals; for a recording exactly 24 hours long, the sampling interval was 329 ms. A "boxcar" low-pass filter with a window twice the sampling interval was then applied. Gaps in the time series resulting from noise or ectopic beats were filled in with linear splines. A fast Fourier transform was computed and the resulting power spectrum was corrected for the attenuating effects of both the filter and the sampling. For a 24-hour recording, the effective frequency range for this method is from 1.157×10^{-5} to 0.800 Hz (periods of seconds to hours). Five frequency domain measures of heart period variability were computed by integrating over their frequency intervals (defined in Table II). In addition, we calculated the ratio of low- to high-frequency power, a measure that has been used as an indicator of sympathovagal balance.[3] High values for the ratio indicate predominance of sympathetic nervous activity.

Time domain measures of heart period variability: From the time series of normal RR intervals, the 6 time domain measures defined in Table II were calculated.

Statistical methods: The frequency distribution of each variable was plotted and assessed for skewness us-

TABLE II Definitions for Time and Frequency Domain Measures of Heart Period Variability

Variable	Domain	Units	Definition
Night-day difference	Time	ms	Difference between the average of all the normal RR intervals at night (24:00 to 05:00) and the average of all the normal RR intervals during the day (07:30 to 21:30)
SDNN	Time	ms	Standard deviation of all normal RR intervals in the entire 24-hour ECG recording
SDANN index	Time	ms	Standard deviation of the average normal RR intervals for all 5-minute segments of a 24-hour ECG recording (each average is weighted by the fraction of the 5 minutes that has normal RR intervals)
SDNN index	Time	ms	Mean of the standard deviations of all normal RR intervals for all 5-minute segments of a 24-hour ECG recording
r-MSSD	Time	ms	Root-mean-square successive difference (the square root of the mean of the squared differences between adjacent normal RR intervals over the entire 24-hour ECG recording)
pNN50	Time	percent	Percentage of differences between adjacent normal RR intervals that are > 50 ms computed over the entire 24-hour ECG recording
Total power	Frequency	ms^2	The energy in the heart period power spectrum up to 0.40 Hz
Ultra low frequency power	Frequency	ms^2	The energy in the heart period power spectrum up to 0.0033 Hz
Very low frequency power	Frequency	ms^2	The energy in the heart period power spectrum between 0.0033 and 0.04 Hz
Low frequency power	Frequency	ms^2	The energy in the heart period power spectrum between 0.04 and 0.15 Hz
High frequency power	Frequency	ms^2	The energy in the heart period power spectrum between 0.15 and 0.40 Hz
LF/HF ratio	Frequency	none	The ratio of low- to high-frequency power

ECG = electrocardiographic; HF = high frequency; LF = low frequency.

ing the value of the standardized third moment around the mean. If the distribution was markedly skewed, i.e., had a skewness coefficient exceeding 1.00, a logarithmic transformation was applied and the new frequency distribution was plotted and examined again. In all cases, the logarithmic transformation did an excellent job of symmetrizing the skewed distributions (see Figure 1) and the log-transformed data were used for those statistical analyses that require data to have a reasonably normal (Gaussian) distribution. We constructed matrices of Pearson product-moment correlation coefficients to evaluate the associations among the measures of heart period variability or between measures of heart period variability and other important predictors of mortality.

When testing hypotheses about the association between 1 or more risk predictors and death, we used the P2L BMDP computer program[13] to perform Cox proportional hazards analyses.[14] For ease of communication and for eventual clinical use, we dichotomized the 6 time domain measures of heart period variability when estimating their association with mortality. For each, we determined the dichotomization point that maximized the hazard ratio from a Cox regression model[14] for comparing patients below the cut point (expected to be at high risk) with those at or above it (expected to be at low risk).

To determine whether any of the 6 time domain measures of heart period variability was significantly associated with mortality, and to estimate their relative strengths of association, we evaluated each measure separately, after dichotomization, in a pair of Cox proportional hazards survival models.[14] First, in a univariate analysis, each measure was analyzed as the sole predictor of mortality. Second, 5 covariates known to predict mortality — age, New York Heart Association functional class, rales in the coronary care unit phase of infarction, left ventricular ejection fraction, and 24-hour average frequency of ventricular arrhythmias — were added to the model to test whether the measure of heart period variability predicted mortality independently of the covariates.

For the Cox analysis that adjusted for other risk predictors, the measures of heart period variability were dichotomized to provide ease of interpretation, but the covariates were coded to provide the best fitting model to predict mortality.[5,15]

Statistical significance was assessed by referring Z, the estimate of the regression coefficient B divided by its standard error, to the standard normal distribution. The strength of association between a measure of heart period variability and a mortality end point was evaluated using exp(B), which can be interpreted as a relative risk for the given measure.

Mortality end points: We estimated the association between the 6 time domain measures of heart period variability and 3 mortality end points: death from all causes, cardiac death, and arrhythmic death by the Hinkle-Thaler definition.[16] When mortality of all causes was the end point, patients were included in the analysis

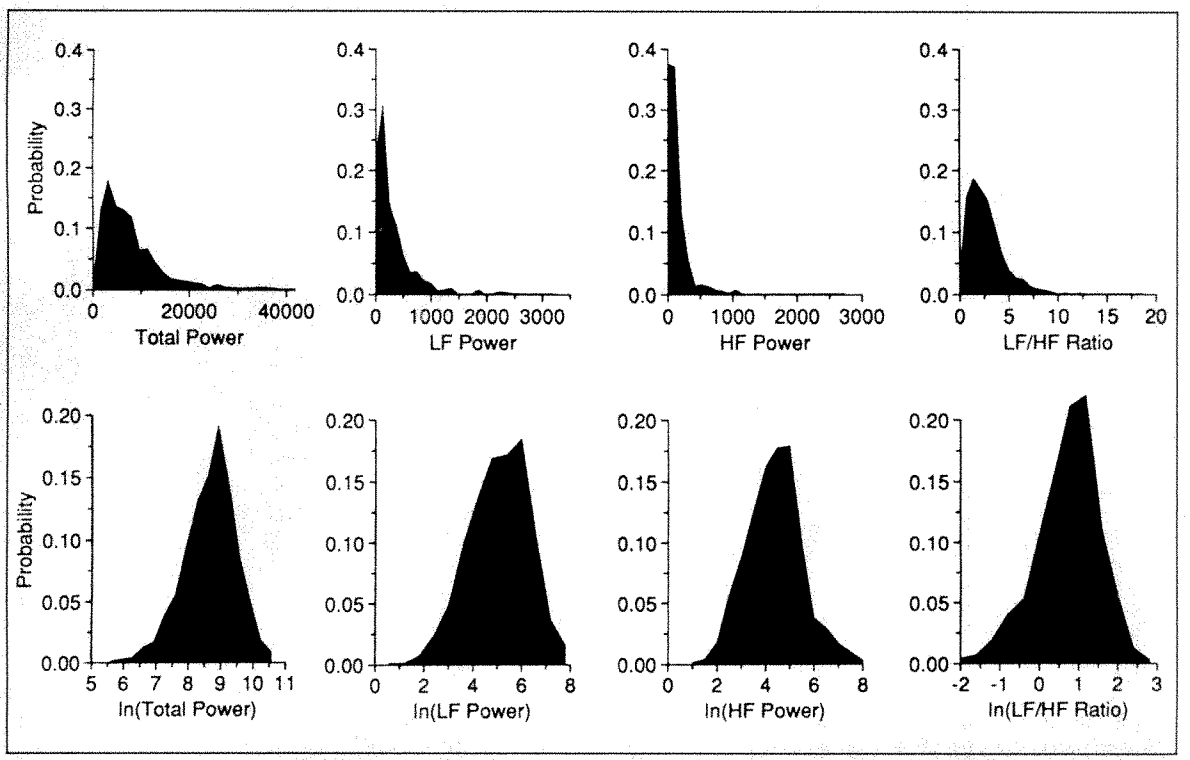


FIGURE 1. The distribution of the components of total power: from left to right, ultra low frequency power (<0.0033 Hz); very low frequency power (0.0033 to 0.04 Hz); low-frequency (LF) power (0.04 to 0.15 Hz); and high-frequency (HF) power (0.15 to 0.40 Hz). *top row*, frequency distributions with the original units of measurement on the X axis, i.e., ms^2. The Y axis is the proportion of the 715 patients with the given value on X. Note that the frequency distributions all are skewed to the right. *bottom row*, frequency distributions of the natural logarithm of the same frequency domain variables. Note that the frequency distributions of the logarithmic transformations have a more Gaussian distribution.

TABLE III Correlations Among Measures of Heart Period Variability (n = 715)

	Night-Day Difference	SDNN	Ln Total Power	Ln ULF Power	SDANN Index	Ln VLF Power	SDNN Index	Ln LF Power	Ln r-MSSD	Ln pNN50	Ln HF Power	Ln LF/HF Power
Night-day difference	1.00											
SDNN	0.71	1.00										
Ln Total power	0.68	0.96	1.00									
Ln ULF power	0.71	0.95	0.99	1.00								
SDANN index	0.75	0.98	0.94	0.96	1.00							
Ln VLF power	0.43	0.78	0.82	0.75	0.68	1.00						
SDNN index	0.44	0.82	0.79	0.71	0.70	0.90	1.00					
Ln LF power	0.42	0.72	0.75	0.67	0.61	0.91	0.89	1.00				
Ln r-MSSD	0.28	0.62	0.58	0.52	0.51	0.60	0.78	0.65	1.00			
Ln pNN50	0.27	0.57	0.56	0.50	0.49	0.59	0.71	0.64	0.93	1.00		
Ln HF power	0.35	0.67	0.66	0.59	0.57	0.70	0.82	0.77	0.92	0.89	1.00	
Ln LF/HF power	0.17	0.20	0.26	0.23	0.17	0.45	0.25	0.49	−0.25	−0.22	−0.18	1.00

Ln = natural logarithm; other abbreviations as in Table II.

as long as they were known to be alive. In analyses of cause-specific mortality, patients who died of other causes were censored at the time they died.

RESULTS

Transformation of heart period variability variables: Figure 1 shows the distributions of the 4 components of total power and illustrates the effect of log transformation in the 715 patients we studied. All of the untransformed frequency domain distributions are positively skewed, as are the distributions for 2 time domain measures, r-MSSD and pNN50 (see explanation in Table II). The distributions of the transformed variables have approximately normal distributions and therefore are suitable for parametric statistical procedures, such as the *t* test, analysis of variance and correlation/regression analyses.

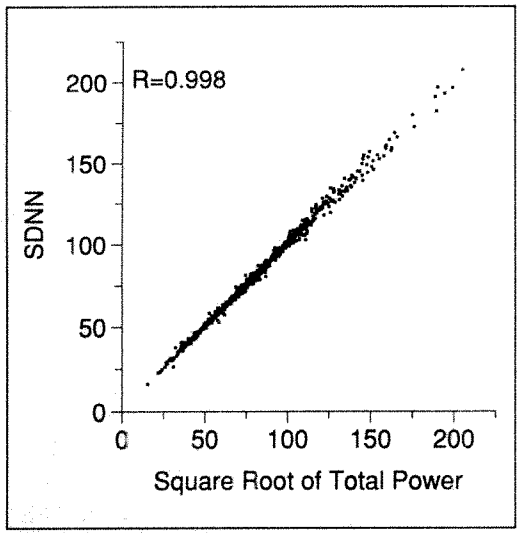


FIGURE 2. The relation between the standard deviation of the normal RR intervals (SDNN) and the square root of total power in the 24-hour heart period power spectrum. The units for both variables are ms. Note that the empirically determined relation is very close to the theoretically expected relation, i.e., intercept of 0 and slope of 1. Also, the correlation coefficient is very close to 1.

Correlations between the measures of heart period variability: Table III presents correlations between frequency and time domain measures of heart period variability. Power in each band in the frequency domain has a corresponding variable in the time domain that correlates so strongly with it ($r \cong 0.90$) that the 2 variables are essentially equivalent: ultra low frequency power with SDNN and SDANN index, very low frequency power and low-frequency power with SDNN index, and high-frequency power with r-MSSD and pNN50. Correlations this strong between 2 variables suggest that the 2 variables can be used interchangeably when being related to a third variable such as death. As expected from theoretical considerations, SDNN and the square root of total power for a 24-hour interval are almost perfectly correlated (see Figure 2), and the regression line essentially has a slope of 1 and an intercept of 0. This indicates that the manipulation of the data and the calculations involved in the power spectral analysis did not distort the data.

There are 3 natural clusters among 10 of the 12 variables in Table III: (1) SDNN, SDANN index, total power, and ultra low frequency power; (2) very low frequency power, low-frequency power, and SDNN index; and (3) high-frequency power, r-MSSD and pNN50. Interestingly, the ratio of the power in the low-frequency band to the power in the high-frequency band does not correlate strongly with any of the other measures of heart period variability, even those that are used to cal-

TABLE IV Percent of Total Power in the Components of the Heart Period Power Spectrum (n = 715)

Component	Frequency Range (Hz)	Mean ± SD	Median	Quartile First	Quartile Third
ULF power	<0.0033	82 ± 8	83	77	89
VLF power	0.0033–0.04	12 ± 6	12	8	16
LF power	0.04–0.15	4 ± 3	3	2	5
HF power	0.15–0.40	2 ± 2	1	1	2

Abbreviations as in Table II.

TABLE V Correlation of Measures of Heart Period Variability with Established Postinfarction Risk Predictors and with the Average Normal RR Interval (n = 715)

	Age	NYHA Functional Class	Rales in the CCU	LVEF	Ln (1 + VPC/hour)	Average Normal RR Interval
Night-day difference	−0.22	−0.13	−0.18	0.18	−0.17	0.21
SDNN	−0.22	−0.14	−0.25	0.27	−0.18	0.56
Ln Total power	−0.21	−0.15	−0.27	0.28	−0.20	0.56
Ln ULF power	−0.18	−0.14	−0.25	0.26	−0.19	0.52
SDANN index	−0.28	−0.18	−0.32	0.30	−0.21	0.58
Ln VLF power	−0.18	−0.13	−0.22	0.26	−0.17	0.50
SDNN index	−0.34	−0.18	−0.32	0.31	−0.22	0.48
Ln LF power	−0.31	−0.14	−0.29	0.27	−0.18	0.59
Ln r-MSSD	−0.15	−0.04	−0.17	0.21	−0.12	0.56
Ln pNN50	−0.16	−0.05	−0.17	0.22	−0.13	0.51
Ln HF power	−0.23	−0.08	−0.23	0.25	−0.19	0.57
Ln LF/HF power	−0.20	−0.18	−0.18	0.13	−0.09	−0.04

CCU = coronary care unit; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VPC = ventricular premature complexes; other abbreviations as in Tables II and III.

culate the ratio. Also, the night-day difference does not correlate strongly with other measures of heart period variability, but correlates moderately with variables that measure low frequency events — SDNN, SDANN index, total power, and ultra low frequency power.

Components of the heart period power spectrum: Table IV partitions the total power into 4 components: ultra low, very low, low-, and high-frequency power. Most of the total power, >80%, is in the ultra low frequency band (<0.0033 Hz). On the average, the 2 bands of the power spectrum with known physiologic significance, i.e., low-frequency and high-frequency power, comprise 4 and 2%, respectively, of the total power in the 24-hour heart period power spectrum. Be-

TABLE VI Cut Points for Time Domain Measures of Heart Period Variability Used for Analysis of Mortality (n = 715)

Variable	Units	Cut Point	Below Cut Point	
			No.	%
Night-day difference in normal RR intervals	ms	40	178	24.9
SDNN	ms	50	103	14.4
SDANN index	ms	40	81	11.3
SDNN index	ms	20	108	15.1
r-MSSD	ms	15	163	22.8
pNN50	%	0.75	130	18.2

Abbreviations as in Table II.

TABLE VII Association of Time Domain Measures of Heart Period Variability with All-Cause, Cardiac and Arrhythmic Mortality

	Mortality					
	All Causes (119 deaths)		Cardiac (88 deaths)		Arrhythmic (68 deaths)	
Variable	Z*	Relative Risk†	Z*	Relative Risk†	Z*	Relative Risk†
Unadjusted for Other Risk Predictors (n = 715)						
Night-day difference	3.41	1.9	2.98	1.9	3.05	2.1
SDNN	5.95	3.3	5.11	3.3	4.57	3.4
SDANN index	6.67	4.0	5.52	3.9	4.68	3.8
SDNN index	5.79	3.2	5.31	3.5	4.43	3.3
r-MSSD	3.08	1.9	3.65	2.3	2.91	2.1
pNN50	3.34	2.0	4.05	2.6	3.28	2.4
Adjusted for Five Other Risk Predictors‡ (n = 673)						
Night-day difference	1.52	1.4	0.79	1.2	1.19	1.4
SDNN	1.99	1.6	1.47	1.5	1.48	1.6
SDANN index	3.23	2.1	2.64	2.0	2.40	2.1
SDNN index	2.19	1.6	1.93	1.7	1.64	1.6
r-MSSD	1.10	1.3	1.59	1.5	1.14	1.4
pNN50	1.48	1.4	2.22	1.7	1.83	1.7

*$Z \geq 1.96$, $p < 0.05$; $Z \geq 2.58$, $p < 0.01$; $Z \geq 3.30$, $p < 0.001$.
†Relative risk = probability of dying if below the cut point/probability of dying if above the cut point.
‡Age, New York Heart Association functional class, rales in the coronary care unit, left ventricular ejection fraction, and frequency of ventricular arrhythmias.
Abbreviations as in Table II

cause of the small fraction of total power in the low- or high-frequency bands, it is possible to obtain a poor correlation between the power in either of these bands and total power, SDNN, or SDANN.

Correlations between heart period variability and other postinfarction risk predictors: The correlations between time and frequency domain measures of heart period variability and previously identified postinfarction risk predictors are remarkably weak (Table V). No r value even reaches 0.40. This lack of correlation provides ample opportunity for measures of heart period variability to improve the fit of multivariate models for predicting risk of death. The 24-hour average normal RR interval, which is not an important risk predictor, has a modest correlation (r values about 0.50) with all measures of heart period variability except the night-day difference and the ratio of low- to high-frequency power.

Prediction of mortality using time domain variables: Table VI lists the 6 variables we evaluated, their units, their optimal cut points, and the numbers of patients in the groups categorized as having low values for the variable. Table VII lists, for each measure of heart period variability, the Z scores and relative risks for the association with the 3 mortality end points determined using Cox regression analysis unadjusted for any covariates. All 715 patients were included in this analysis. The measures of heart period variability were dichotomized (Table VI). Each time domain measure of heart period variability had a significant ($p < 0.05$) and most had a strong univariate association (relative risk ≥ 2) with each of the mortality end points. SDANN index, which is strongly associated with ultra low frequency power, had a significant and strong association with all 3 mortality end points. SDNN index, which is strongly associated with very low frequency and low frequency power, also had a significant and strong association with each of the 3 mortality end points. r-MSSD and pNN50, which are strongly associated with high-frequency power, had a significant and moderately strong association with the 3 mortality end points, but the associations were weaker than for the other variables. In a multivari-

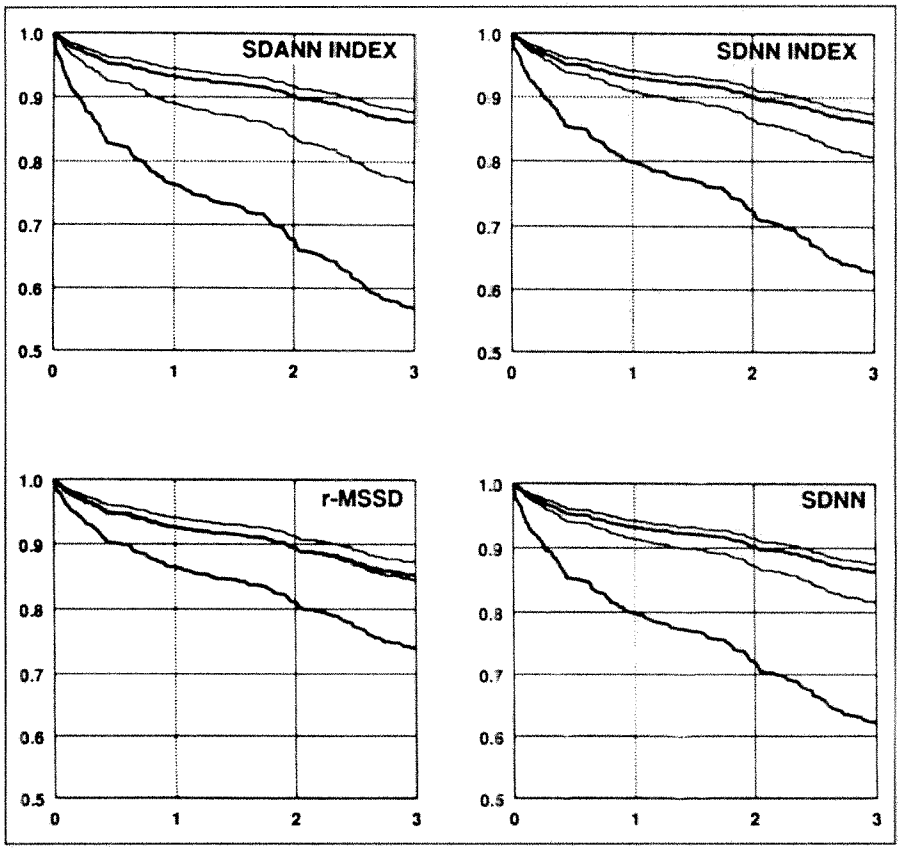


FIGURE 3. Survival curves for patients in the high or low category for 4 time domain measures of heart period variability, SDANN index, SDNN index, and r-MSSD and SDNN, using all-cause mortality as the end point. These curves were fitted by Cox's method for the 673 patients who had adequate Holter data and values for all 5 covariates. *Thick lines* represent unadjusted heart period variability data, *thin lines* represent data adjusted for the covariates: age, New York Heart Association functional class, rales in the coronary care unit, radionuclide ejection fraction, and the frequency of ventricular premature complexes. In *each panel,* the *top 2 curves* are for patients in the high category and the lower 2 are for patients in the low category. The numbers of patients at the start of follow-up, and the numbers known to be alive and being followed after 1, 2 and 3 years were as follows: high SDANN index (≥40 ms) — 596, 546, 506, 228; low SDANN index (<40 ms) — 77, 60, 49, 21; high SDNN index (≥20 ms) — 573, 531, 492, 221; low SDNN index (<20 ms) — 100, 75, 63, 28; high r-MSSD (≥15 ms) — 522, 477, 440, 208; low r-MSSD (<15 ms) — 151, 129, 115, 41; high SDNN (≥50 ms) — 577, 527, 490, 223; low SDNN (<50 ms) — 96, 78, 65, 26.

ate Cox regression analysis using a step-up approach to evaluate the independent association of the time domain measures of heart period variability with death of all-causes (not adjusted for the covariates), SDANN index was selected first, i.e., had the strongest association with death, and SDNN index was selected second. With SDANN and SDNN indexes in the Cox regression model, the addition of the other variables, singly or together, did not significantly improve the prediction of all-cause mortality.

Prediction of mortality using time domain variables adjusting for previously described postinfarction risk predictors: Figure 3 shows survival curves for 4 time domain components of heart period variability calculated using the Cox regression method before and after adjusting for the 5 covariates. Table VII lists, for each measure of heart period variability, the Z scores and relative risks for the 3 mortality end points, determined using Cox regression analysis to adjust for the 5 risk predictor covariates. The 673 patients who had an adequate Holter recording and measurements on all 5 covariates were included in this analysis. Measures of heart period variability were dichotomized (Table VI). After adjustment, some of the variables were no longer significantly associated with mortality. The association between all-cause mortality and SDNN, and SDANN and SDNN indexes remained significant and moderately strong, whereas r-MSSD and pNN50 were only weakly associated with mortality after adjustment.

DISCUSSION

Patterns of correlations among measures of heart period variability: There are strong correlations between frequency and time domain measures of heart period variability. The patterns of correlations are informative. For every band of the 24-hour heart period power spectrum, there is a strong correlation ($\cong$0.90) with at least 1 time domain measure of heart period variability, indicating that they may be controlled by similar influences. In the power spectral literature, the physiologic significance of high- and low-frequency power has been delineated. High-frequency power is a pure vagal signal and its frequency is modulated by the frequency of breathing.[2,3] Low-frequency power is a mixed vagal and sympathetic signal and its amplitude is increased by either increases in vagal tone or increases in sympathetic activity, especially when the autonomic nervous system is participating in arterial baroreflexes.[2,3] Low- and high-frequency powers have a moderate correlation (r = 0.77). In an experiment conducted in normal human subjects, we showed that low- and high-frequency power increase in parallel when vagal tone is increased by atenolol treatment.[17] Also, we showed that low- and high-frequency power decrease in parallel during silent myocardial ischemia in ambulatory patients with known coronary heart disease; this finding was interpreted as withdrawal of vagus nerve activity.[18] These findings suggest that, over a 24-hour period, both low- and high-frequency bands in the heart period power spectrum predominantly reflect parasympathetic activity. However, short-term measurement (e.g., over 5 minutes) of the heart period power spectrum in conjunction with controlled barostress provides important information about the sympathetic nervous system.[2,3]

In normal subjects, a change in posture from lying to standing[2] or head-up tilt from 0° to 90°[3] causes a decrease in the high-frequency power and a substantial increase in the ratio of low- to high-frequency power, indicating a decrease in vagal modulation of the RR interval and an increase in sympathetic nervous system activity. This interpretation is strengthened by the response to β-adrenergic blocking drugs which prevent, or markedly attenuate, the increase in the ratio of low- to high-frequency power with postural stress.[2,3] The findings in this study show that some of the time domain measures of heart period variability also are influenced by autonomic nervous system activity: SDNN index provides similar information to low-frequency power and r-MSSD and pNN50 provide information similar to high-frequency power.

Potential for heart period variability to predict death and its mechanisms after myocardial infarction: Since time domain measures of heart period variability are strongly associated with frequency domain measures (already shown to predict mortality[5]), it is no surprise that time domain measures also predict mortality in the 3 years after myocardial infarction. Which measures of heart period of variability are to be used is largely a matter of objectives and convenience. For risk stratification, ultra low frequency power, very low frequency power, SDNN, SDANN index, and SDNN index provide the best prediction. For mechanistic studies, low-frequency power, SDNN index, high-frequency power, r-MSSD and pNN50 provide insight into the status of the autonomic nervous system.

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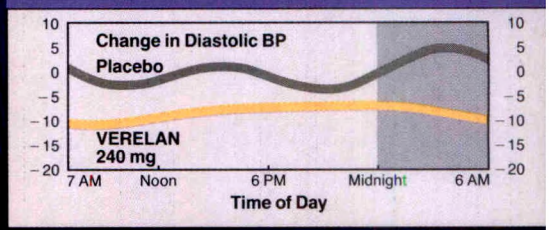
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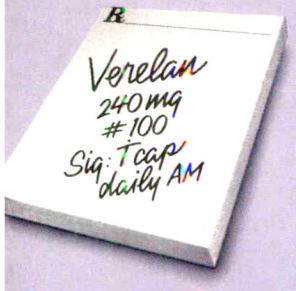
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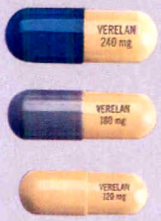
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References: 1. Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol.* 1991;31:144-150. 2. Data on file for VERELAN 240 mg, Lederle Laboratories, Pearl River, NY.

Brief Summary

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For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can

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increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitali toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clea ance of digitoxin. The digoxin dose should be reduced when verapamil is given and the patient carefull monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-lowerin agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administratior Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV cor duction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic ca diomyopathy should be avoided, since significant hypotension may result. Verapamil has been give concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction be tween cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clea ance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must b monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce ver pamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum le els of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs caref titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromusc lar blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal ca cinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, ar verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and we controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during ver pamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been establishe

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently r ported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adver reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspe sia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater tha 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headacl (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); A block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, ma keting experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atrioventric lar dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncop **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lyr phatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disc ders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respirator** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticar Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynec mastia, impotence, increased urination, spotty menstruation.

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Survival After Implantation of the Cardioverter Defibrillator

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The actuarial survival of 60 consecutive recipients of the implanted cardioverter defibrillator (ICD) were compared with 120 matched concurrent medically treated patients using a case-control design. All ICD patients and controls presented with either sustained ventricular tachycardia or ventricular fibrillation. Controls were matched to ICD recipients according to 5 variables: age, left ventricular ejection fraction, arrhythmia at presentation, underlying heart disease and drug therapy status. Mean ages were 58 and 59 years in ICD patients and controls, and the average ejection fractions were 36 and 35%. Coronary artery disease was present in 75 and 79% of ICD patients and controls, respectively. During follow-up, sudden deaths were fewer in ICD recipients than in controls (5 vs 10%, $p < 0.01$). At 1 and 3 years, actuarial survival was 0.89 vs 0.72 and 0.65 vs 0.49 for ICD recipients and controls. The 5-year actuarial survival curves were significantly different by the Cox proportional hazards model ($p < 0.05$). It is concluded that in this retrospective case-control study, the use of the ICD in the management of patients at risk for sudden death results in improved probability of survival.

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The implanted cardioverter defibrillator (ICD) appears to be effective in preventing sudden cardiac death due to recurrent life-threatening ventricular dysrhythmias.[1,2] There have been no prospective controlled studies to define the impact of the device on patient survival.[3] A retrospective analysis showed a decreased mortality with the use of the ICD in a subset of patients presenting with poorly tolerated tachyarrhythmias.[4] To date, the efficacy of the device has been inferred by 2 methods. The first is based on the low incidence of sudden death recurrence.[5–7] Whether reduction in the rate of sudden death results in altered patient survival or quality of life is unclear from data of this nature, although comparisons have been made to other descriptive studies that used other therapies.[8] The second method compares the observed and hypothetical survivorships using device discharge as a substitute for out-of-hospital sudden death.[9–12]

Although future devices may allow storage and telemetry of the rhythm preceding an event, most models currently implanted do not allow assessment of the circumstances surrounding an ICD shock. Although reasonable "rules"[12] have been developed with which to evaluate a discharge, there remains the concern that not all, even symptomatic, episodes of ICD discharge represent a rescue from what would otherwise have been an episode of sudden cardiac death.[10] Other investigators have found that 9 to 21% of discharges are for causes other than sustained ventricular tachyarrhythmias or ventricular fibrillation.[5,13]

We used a retrospective case-control technique to assess the impact of ICD insertion on patient survival.

METHODS

The ICD patients in this study were the first 60 consecutive ICD recipients to receive implants and followed up at Moffitt Hospital, University of California, San Francisco from March 1983 to January 1989. All patients received an Intec Systems model B or a CPI (Cardiac Pacemaker, Inc., St. Paul, Minnesota) Ventak series ICD.

The control patients were drawn from a database accumulated at the same institution consisting of >500 patients presenting with sustained ventricular tachycardia or aborted sudden death who were treated medically. Detailed characteristics and outcomes of the patients in this database who received amiodarone have been previously published.[14] Each ICD patient was matched to 2 controls according to 5 clinical variables. Where >2 controls fitting the characteristics were available for matching, a random number table was used. Entry

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TABLE I ICD Patients and Their Controls: Indications and Matching

Indications for ICD Implantation	No. (%)	Controls*	No.	Follow-Up in Control Group†
Clinical recurrence, amiodarone continued	12 (20)	Clinical recurrence on amiodarone	24	Since recurrence
Amiodarone toxicity, amiodarone discontinued‡	19 (32)	Discontinued amiodarone for toxicity, maintained on best alternate medical therapy	38	Since discontinuation
Poor prognosis amiodarone continued§	18 (30)	On amiodarone	36	Since starting amiodarone; ICD added to therapy shortly after initiation of amiodarone in ICD patients
As primary therapy, not on amiodarone	11 (18)	On amiodarone	22	Since starting amiodarone
Total	60 (100)		120	

*All ICD patients were matched to controls according to age (±5 years), ejection fraction (±5%), heart disease and presenting arrhythmia.
†Follow-up among the ICD group is from the time of implantation.
‡Seventeen patients with pulmonary and 2 with neurologic amiodarone toxicity.
§Eight patients with nonsustained ventricular tachycardia on monitor, and 10 with poorly tolerated induced arrhythmias.
ICD = implantable cardioverter defibrillator.

dates for controls ranged from January 1979 to December 1987.

Matching variables: The variables used for matching were age (±5 years), left ventricular ejection fraction (± 5%), type of underlying heart disease, presenting arrhythmia (sustained ventricular tachycardia or sudden cardiac death) and drug therapy status (see next paragraph).

To control for selection bias due to dissimilarities in response to antiarrhythmic drugs, we matched ICD recipients and controls in a category termed drug therapy status. ICD patients received their defibrillator for 1 of 4 indications: (1) development of amiodarone toxicity that required its discontinuation, (2) recurrence of a clinically significant arrhythmic event while receiving amiodarone, (3) presence of what was considered to represent poor prognostic signs of sudden death despite amiodarone therapy, or (4) as therapy of first choice.

Defibrillator recipients who had as their indication for implantation the development of amiodarone toxic effects (most frequently pulmonary toxicity) were matched to controls who also had discontinued amiodarone because of adverse effects but received another medical therapy. Patients who had an ICD added to their amiodarone therapy because of a clinical arrhythmia recurrence while taking amiodarone were matched to controls who also had a recurrence of their dysrhythmia but did not receive an ICD. In both of these subgroups, controls and ICD patients had received amiodarone for a similar period of time before the event which dictated implantation of the ICD.

Some ICD patients received an ICD shortly after starting amiodarone because of concern that they represented a group at particular risk. Early in the study, this was established by the presence of poor left ventricular function and nonsustained ventricular tachycardia on ambulatory monitoring while treated with amiodarone.[15,16] Recently, the induction at electrophysiology study of a poorly tolerated ventricular tachyarrhythmia while receiving amiodarone has been used to identify a group with a poor prognosis warranting implantation of an ICD.[17-19] These patients had all received a net of 10 to 12 g of oral/intravenous amiodarone before the study. Our ICD patients were matched with controls having similar characteristics but who did not receive an ICD.

A final group received ICD as initial therapy. This most often occurred in patients with minimal structural heart disease or at the patients' request. These patients were matched to controls treated with amiodarone.

For ICD patients, follow-up was initiated from the time of implantation of the ICD and include intra- and perioperative deaths. No one died while awaiting a scheduled ICD. Follow-up for controls was begun from the point at which an ICD would have been implanted (i.e., clinical recurrence or toxicity requiring discontinuation).

Statistical analysis: Actuarial survival curves were constructed for controls and ICD patients.[20] The overall probability of survival was estimated using a Cox proportional hazards model.[21] Patients were withdrawn from further analysis when they reached the end of their actual follow-up period or if the device was removed for any reason.

RESULTS

Among the ICD recipients, 19 received their device after toxicity necessitated discontinuation of amiodarone. Pulmonary toxicity was present in 17 patients, and neurotoxicity in 2. Twelve patients received their device because of a clinical recurrence while receiving amiodarone. All 12 continued to take amiodarone after the ICD was implanted. Eighteen patients received their device because of concerns over their poor prognosis. This included 8 patients with low ejection fractions who continued to have nonsustained ventricular tachycardia after oral loading with amiodarone, and 10 patients with poorly tolerated induced arrhythmias at invasive electrophysiologic study after amiodarone loading. Finally, 11 received their device as primary therapy. Of these, 2 patients were also receiving β blockers (Table I).

No ICD patients or controls received surgical or catheter ablative procedures for the treatment of their arrhythmia. The 38 controls who discontinued amiodarone for reasons of drug toxicity were maintained on a variety of investigational or conventional antiarrhythmic medications. These were chosen either by serial electrophysiologic testing as those that led to the greatest slowing of induced arrhythmia or on the basis of suppression of ambient ectopy. The 24 controls who had an arrhythmia recurrence while taking amiodarone did not have systematic changes in drug therapy. All continued

to take amiodarone. The control subgroups who were matched to ICD patients who received an ICD for prognostic reasons or as primary therapy were taking amiodarone as their sole antiarrhythmic therapy.

There were no significant differences between ICD patients and controls with respect to age, ejection fraction, presenting arrhythmia or underlying heart disease (Table II). Seventy-five percent of both groups had coronary artery disease and over half had an episode of aborted sudden death as their presenting clinical dysrhythmia. The mean ejection fraction was 35 ± 11% among controls and 36 ± 12% for ICD patients, and both groups were largely concurrent. The mean year of entry into the study was 2.8 years later for ICD compared with control patients. Seventy-seven percent of controls were entered into the study during the same time period as ICD patients.

During follow-up there have been 13 and 59 deaths among the ICD patients and their matched controls, respectively. Death was sudden in 3 ICD recipients and in 12 control patients ($p < 0.01$ chi-square).

Of the 13 deaths in the ICD group, 2 were perioperative. Congestive heart failure was the most frequent cause of death occurring in 7 patients. One patient died of complications from a stroke. Three deaths were sudden and likely due to arrhythmias. In 2 patients, the devices were retrieved, were functional and had been discharged since the previous clinical evaluation. Only one of the sudden deaths occurred in the first 24 months of follow-up in the ICD group. The actuarial survival curves for both sudden and all-cause death in the ICD group are shown in Figure 1.

The cumulative probability of survival (all causes of death) between the 2 groups is compared in Figure 2. The 1- and 3-year actuarial survival for ICD recipients was 0.89 and 0.65. The 1- and 3-year actuarial survival for controls was 0.72 and 0.49. The mean follow-up was 23.5 ± 19.7 months for controls (mean ± SD, range 1 to 98, median 20) and 18.5 ± 15.1 months for the ICD recipients (range 1 to 70, median 15).

TABLE II Comparison of ICD Recipients and Their Controls

	ICD Recipients (n = 60)	Controls (n = 120)
Age (yr)	58 ± 15	59 ± 14
Ejection fraction (%)	36 ± 12	35 ± 11
Heart disease (%)		
CAD	75	79
IDC	20	15
Arrhythmias (%)		
ASD	59	57
VT	41	43
Follow-up (mos)	18.5 ± 15.1	23.5 ± 19.7

ASD = aborted sudden death; CAD = coronary artery disease; ICD = implanted cardioverter defibrillator; IDC = idiopathic dilated cardiomyopathy; VT = ventricular tachycardia.

By the Cox proportional hazards model there was a significant difference between the 2 survivorships when followed to 60 months (1 sided test, $Z = -1.87$, $p < 0.05$). Figure 2 shows that the 2 curves diverge in their initial portions and converge by 40 months.

Subgroup analysis was performed for ICD recipients and their matched controls with an ejection fraction > and <25%. The trend of the results was similar to those illustrated in Figure 2, although differences were not significant. There was also a trend toward a greater benefit in survival among the ICD subgroup who discontinued amiodarone compared with controls managed with other medical therapy after discontinuation of amiodarone.

DISCUSSION

This study has shown that implantation of the ICD has a significant impact on mortality among a group of

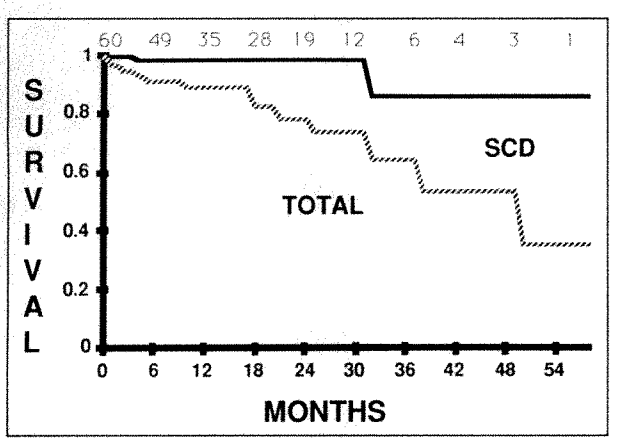


FIGURE 1. Actuarial survival among the 60 recipients of an implantable cardioverter defibrillator. *Upper solid curve* describes the probability of freedom from arrhythmic sudden death. *Lower shaded curve* describes the probability of survival for the entire group. The numbers at the *top* of the graph refer to the number of patients available for follow-up in the implantable cardioverter defibrillator group in 6-month intervals. See text for discussion. SCD = sudden cardiac death; TOTAL = total mortality.

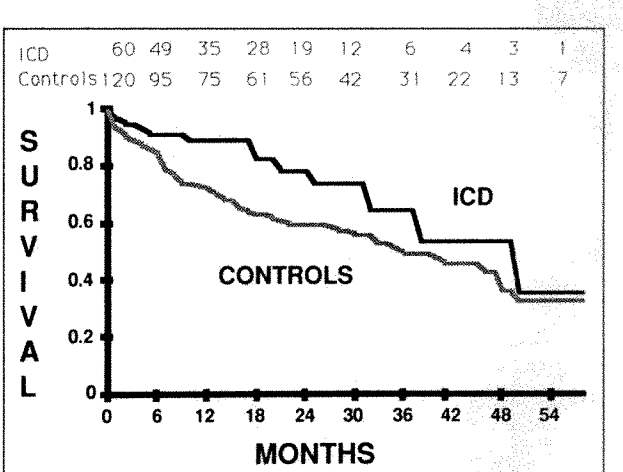


FIGURE 2. Actuarial survival between the 2 groups. *Upper solid curve* describes the probability of survival in the implantable cardioverter defibrillator (ICD) group and is a reproduction of the *lower curve* of Figure 1. *Lower shaded curve* describes the probability of survival among the 120 matched controls. The numbers at the *top* of the graph refer to the number of patients available for follow-up in the ICD group *(top row)* and in the control group *(bottom row)* in 6-month intervals. See text for discussion. CONTROLS = controls matched to ICD cases.

patients with impaired left ventricular function (mean ejection fraction of 35%). The only other study to compare survival between ICD recipients and a control population found a survival advantage in patients who had a poorly tolerated ventricular dysrhythmia at presentation.[4] That study included 21 patients treated with an ICD and was, like the present study, performed at a single institution, and with physician preference and device availability dictating who would receive an ICD.

Our findings may not be applicable to all ICD recipients. This depends on the degree to which the cases in this report represent the population of patients for whom the ICD is indicated. Though the present report has a smaller number of ICD recipients, their survival is equivalent to larger series having a similar duration of follow-up. The overall actuarial survival of the ICD patients (Figure 1) is 0.89, 0.78 and 0.65 at 12, 24 and 36 months, respectively. This is comparable with survival rates of 0.87, 0.78 and 0.74 among 180 patients reported by Guarnieri et al,[6] though it is lower than the survival of 0.91, 0.85 and 0.82 for the same times among the 270 ICD recipients reported by Winkle et al.[5] The latter may reflect differences in patient selection among implanting centers. Our 1-, 2- and 3-year actuarial probability of freedom from recurrent sudden death of 0.98, 0.98 and 0.86 is also comparable to other published series.[5-7,13]

In addition to the similarities in both total and sudden death mortality, the patients in this report were of similar age and comparable ventricular function to those in larger series. In the study of Winkle et al[5] the average age of recipients was 58 ± 12 years and their median ejection fraction was 34 ± 15%, whereas in the series described by Guarnieri et al[6] the average age was 55 years with a mean ejection fraction of 36%.

Our results suggest that insertion of the ICD conveys a survival advantage. Over time, this survival advantage will dissipate and deaths due to progressive heart failure finally offset the gains made by prompt and effective prevention of sudden arrhythmic deaths. The point at which this occurs cannot be determined from our study owing to small sample size and limited follow-up duration. The meaning this has for optimal patient selection requires further exploration.

One objective of this study was to control for medical therapy. Half of the ICD and 68% of the control patients received amiodarone during the study period (Table I). Neither the ICD subgroup nor controls who had amiodarone toxicity received the drug during the study period. The study is a comparison of amiodarone versus the ICD only for the small group of 11 ICD patients receiving their device as primary therapy. They were matched to controls receiving amiodarone as primary therapy. This was done on the basis that amiodarone represented the best medical alternative for these patients.[14,22,23]

In a retrospective study such as this, there may be other factors that dictated who would receive an ICD which are not compensated for by the matching process. This is especially true in the case of patients who received investigational devices before approval of the Food and Drug Administration and ready availability of the ICD. In addition, there was a 2.8 year lag between the time of entry of ICD and patients into this study. This may mean that other important variables that affect mortality such as use of β blockers, angiotensin-converting enzyme inhibitors, aspirin or type IC antiarrhythmic agents may not have been equally divided between the 2 groups. We have compared the 2 survival curves with appropriate weighting for the sample size at any one time but did not correct for these or other covariables that may affect a study such as this.

As a result, the clinical significance that can be inferred from the results of our study require verification in a larger prospective study. This is underscored by an earlier analysis with a smaller sample size that did not find a statistically significant difference in actuarial survival between ICD recipients and controls.[24] In addition, preliminary results from a prospective randomized study of the ICD failed to find a significant impact on survival compared with medical therapy.[25]

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Head-Upright Tilt-Table Testing in Evaluation and Management of the Malignant Vasovagal Syndrome

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Vasovagally mediated cardiac asystole has been proposed as a potential cause of sudden cardiac death. To assess this possibility and identify characteristics that define patients with vasovagally mediated asystole, head-upright tilt-table testing was performed in 50 consecutive patients (26 women and 24 men, mean age 42 ± 10 years) with recurrent unexplained syncope. The upright tilt-table test was performed in the fasting state for 30 minutes, with or without the use of intravenous isoproterenol (1 to 3 μg/min). The production of ventricular asystole lasting >4 seconds was considered a positive result. All patients with tilt-induced asystole received therapy with either β blockers, disopyramide, transdermal scopolamine or atrioventricular permanent pacing, the efficacy of which was evaluated with serial tilt-table tests. Reproducible tilt-induced asystole occurred in 10 patients (7 men and 3 women, mean age 23 ± 12 years) (7 patients during baseline tilt, and 3 during isoproterenol infusion). Analysis of this group revealed that they had significantly more frequent and severe syncopal episodes (3 patients had episodes needing bystander cardiopulmonary resuscitation) than did those patients with tilt-induced syncope without asystole. All patients who had tilt-induced asystole eventually became tilt-table negative with therapy (4 with β blockers, 2 with disopyramide, and 4 with atrioventricular permanent pacing), and over a mean follow-up of 21 ± 6 months no further syncopal episodes occurred. It is concluded that patients with recurrent tilt-induced asystole represent a distinct subgroup that has recurrent severe syncope that may mimic or result in sudden cardiac death. Head-upright tilt-table testing is clinically useful in the diagnosis of this malignant vasovagal syndrome and in the evaluation of prophylactic therapy.

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Although originally thought to be a benign disorder,[1] Milstein et al[2] reported that episodes of life-threating cardiac asystole may occur as an extreme manifestation of vasovagal syncope and may lead to or mimic the sudden cardiac death syndrome. Maloney et al[3] used the term malignant vasovagal syncope to describe this subgroup of patients. The present study investigated the clinical use of head-upright tilt-table testing in the identification of patients with the malignant vasovagal syndrome and examined the outcomes of pharmacologic versus pacemaker therapy.

METHODS

Fifty consecutive patients (26 women and 24 men, mean age 42 ± 10 years, range 8 to 62) with history of recurrent syncope of unexplained origin were included in this study. Patients were included in this study if they had ≥2 episodes of syncope during the preceding 6 months, the cause of which remained unknown despite a thorough history and physical examination, a 12-lead electrocardiogram, ambulatory electrocardiographic monitoring, exercise tolerance test, echocardiography, and a complete neurologic examination that included an electroencephalogram and computed axial tomography of the brain. Sixteen patients also underwent magnetic resonance imaging of the brain. In addition to noninvasive studies, 7 patients underwent coronary angiography, and 18 underwent electrophysiologic studies. The exact details of these investigations are described elsewhere.[4] Each patient also underwent carotid sinus massage for 5 seconds on each side of the neck separately with continuous electrocardiographic monitoring (a positive test was considered as the production of ventricular asystole lasting >3 seconds).

The tilt-table test was performed in the fasting state. All cardioactive medications were terminated ≥5 half-lives before the study. Each patient was connected to a standard cardiographic monitor for continuous evaluation of heart rate and rhythm, and a standard sphygmomanometer was used for blood pressure measurements. After baseline measurements of heart rate and blood pressure, each patient was positioned at an angle 80° from horizontal for up to 30 minutes on a tilt table with a foot board made for weight bearing. Blood pressure measurements were obtained every 3 minutes, and electrocardiographic monitoring was performed continuously. If bradycardia or hypotension, or both, developed during the tilt, the table was rapidly lowered to the su-

TABLE I Response to Head-Upright Tilt

Pt.	Age (yr) & Sex	Total No. of Syncopal Episodes	Tilt-Table Phase Causing Asystole (tilt I/tilt II)	Standing Time in Phase Causing Asystole (min) (tilt I/tilt II)	Length of Asystole During Tilt (sec) (tilt I/tilt II)	Therapy
1	14M	4	Baseline/baseline	25/18	6/7	β blocker
2	19M	8	Baseline/baseline	13/12	10/8	Pacemaker + ergotamine
3	23M	12	Baseline/baseline	10/8	8/5	Pacemaker + ergotamine
4	15F	5	Baseline/isoproterenol (1 μg/min)	28/21	5/7	β blocker
5	35M	7	Baseline/baseline	18/12	12/8	Pacemaker
6	8M	8	Isoproterenol (1 μg/min)/isoproterenol (1 μg/min)	20/15	7/5	Pacemaker
7	22F	4	Isoproterenol (1 μg/min)/isoproterenol (2 μg/min)	17/3	6.5/7	Disopyramide
8	32M	4	Baseline/–	7/–	7/–	Disopyramide
9	40M	10	Baseline/–	4/–	36/–	β blocker
10	26F	5	Isoproterenol (1 μg/min)/isoproterenol (1 μg/min)	21/6	6.5/4	β blocker

pine position, and the study was ended. If no syncope occurred during the initial tilt, the table was lowered to the supine position for 5 minutes, and an intravenous infusion of isoproterenol was begun at 1 μg/min and continued for 5 minutes with the patient supine. Head-upright tilt was then performed as described previously for a period of 30 minutes. If the result of the test was again negative, the patient was returned to the supine position, isoproterenol infusion was increased to 2 μg/min, and head-upright tilt was again performed. If no syncope occurred, isoproterenol infusion was increased to 3 μg/min, and upright tilt was again performed. For the purpose of this study, a positive test was defined as the occurrence of ventricular asystole lasting >4 seconds associated with loss of consciousness.

Therapeutic trials: Each patient with prolonged asystole or complete heart block induced during head-upright tilt-table testing received medical therapy and underwent subsequent tilt-table studies to assess the efficacy of therapy. The following agents were used in this order: metoprolol (50 mg orally) twice daily, transdermal scopolamine patch every 3 days, and sustained release disopyramide (100 mg orally) twice daily. Restudy was performed 4 to 14 days after the initiation of therapy. Failure was defined as recurrence of syncope at the same phase as in the initial study, and success was defined as the prevention of syncope. Testing was terminated when a therapy was found that prevented upright tilt-induced syncope. If the aforementioned agents were unsuccessful in preventing upright tilt-induced syncope or if the patient was intolerant to the medication, a temporary atrioventricular pacemaker was placed percutaneously through the right subclavian vein, and tilt testing was again performed. Separate tilt studies were performed with ventricular pacing only at 70 pulses/min and later during atrioventricular sequential pacing at 70 pulses/min. If temporary pacing was shown to be effective in preventing upright tilt-induced syncope, the patient then underwent permanent atrial ventricular (DDD) pacemaker insertion. Two days after insertion, these patients underwent head-upright tilt-table testing again with pacing rates set at 70 pulses/min. In patients with a dual-chamber pacemaker who continued to have hypotension during head-upright tilt, a 2 mg dose of sublingual ergotamine tartate was administered as prodromal symptoms developed during head-upright tilt.

Statistical analysis: Statistical analysis was used to document the response of patients with recurrent syncope to tilt-table testing, and to determine if they could be distinguished based on their response to tilt-table testing. Patients were grouped according to whether they had asystole or syncope during the tilt-table procedure. Kruskal-Wallis 1-way analysis of variance by ranks was used to compare the groups according to severity of symptoms based on the number of syncopal episodes within the 6 months before the study. All study results are expressed as mean ± SD, and a p value <0.05 was considered statistically significant.

RESULTS

Of the 55 patients examined in this study, 10 had positive tests as defined by the production of ventricular asystole lasting >4 seconds associated with loss of consciousness. Twenty-five patients had syncope during upright tilt testing associated with hypotension or bradycardia, or both, but without asystole. The 10 patients with tilt-induced asystole included 7 men and 3 women, mean age 23 ± 12 years. Nine of these patients had no evidence of organic heart disease or cerebrovascular disease on noninvasive study, and 1 had evidence of mitral valve prolapse on echocardiography. The resting electrocardiogram was normal in all 10 patients. Electrophysiologic study was normal in the 4 patients who underwent this procedure, and the coronary arteries were normal in the 1 who underwent angiography. Each patient with tilt-induced asystole had a long-standing history of severe syncopal symptoms. Comparison of these 10 patients with the 25 who had tilt-induced syncope without asystole, and with the 15 tilt-negative ones showed that those with asystole had significantly more episodes in the 6 months before the study (6.7/patient with asystole, 4.2 with tilt-induced syncope without asystole, and 2.4 with tilt negative; $p < 0.001$).

In the patients with tilt-induced asystole, clinical syncopal episodes were described as a sudden complete loss of consciousness that occurred without warning,

and lasted between 1 and 8 minutes (based on eyewitness accounts). Each of the 10 patients had had some form of bodily injury during syncope, including fractures of the wrist, arms, skull and nose. Three patients had received bystander cardiopulmonary resuscitation for several minutes during episodes, but were awake and in sinus rhythm when paramedic personnel arrived. Two patients were in motor vehicle accidents and lost consciousness while driving. In contrast, only 1 of the 25 patients with tilt-induced syncope without asystole had ever had bodily injury, and none had ever undergone bystander cardiopulmonary resuscitation or lost consciousness while driving.

Responses to head-upright tilt (Table I): In response to head-upright tilt-table testing alone (baseline), 7 patients developed syncope associated with ventricular asystole lasting >4 seconds (Figure 1). Mean time to syncope was 12 ± 11 minutes. The remaining patients were asymptomatic, with appropriate heart rate and blood pressure responses to the baseline tilt. In response to the graded isoproterenol infusion, 3 other patients developed asystole during infusion of 1 μg/min. Mean time to syncope in these 3 patients was 19 ± 2 seconds. Mean asystolic period in all 10 patients was 10 ± 9 seconds. In 8 of the 10 patients, a second drug-free tilt-table test was performed. In each of these patients, asystolic episodes could be reproduced, although 2 needed higher levels of provocation than during the initial study (Table I). Two patients had spontaneous syncopal episodes while being monitored in the hospital after the initial head-upright tilt-table study. Each of these patients was documented to have prolonged asystole during spontaneous syncopal episodes (12 seconds in 1, and 22 seconds in the other).

Responses to therapy: Of the 10 patients with tilt-induced asystole, 6 could be successfully managed by pharmacotherapy alone, 4 with β blockers, and 2 with disopyramide. Not all drugs were tested in each patient. Transdermal scopolamine was not tolerated in 3 patients due to side effects (blurred vision, dry mouth and altered mental states).

Four patients needed permanent pacemaker insertion. In each of these patients, ventricular pacing alone was not as effective as atrioventricular sequential pacing in preventing head-upright tilt-induced syncope. In 2 of these patients, atrioventricular sequential pacing did not completely prevent head-upright tilt-induced syncope from occurring. Rather, the episodes were converted from a sudden dramatic loss of consciousness that would occur without warning (i.e., "drop attacks") to a gradual decrease in blood pressure over a 10-minute period, which the patient was easily able to perceive at its onset. In these 2 patients, the sublingual administration of a 2 mg sublingual ergotamine tartate tablet (Ergostat) completely aborted the hypotensive episode. After a mean follow-up of 21 months, no patient who was tilt-table negative by pharmacotherapy or pacing had had any further full syncopal episodes, and each was able to resume a normal life. The 2 patients who were administered sublingual ergotamine tartate have had to use it to abort syncopal episodes (3 occasions in 1, and 4 in the other) with complete success.

DISCUSSION

Previously, vasovagal syncope was assumed to be a benign disorder with a benign prognosis.[5] However, it has become increasingly apparent that there is a specific subgroup of subjects in whom the disorder may cause major disability and potential death.[2,3] Although the most frequently documented cause of sudden death is ventricular tachyarrhythmia, severe bradycardia has been demonstrated as the cause of cardiovascular collapse in a small percentage of patients.[6,7]

The present study demonstrated 2 important points. First, the head-upright tilt-table test (either alone or combined with isoproterenol infusion) successfully identifies patients with vasovagally mediated asystole, and thereby allows better classification of the disorder. This group (whose disorder we have referred to as the malignant vasovagal syndrome) comprised subjects with recurrent severe syncopal episodes often occurring without prodromata, which are disabling and may occasionally mimic sudden death. These patients demonstrate prolonged periods of asystole during head-upright tilt-table testing lasting >4 seconds and averaging 10 ± 9 seconds in duration (the 4-second cutoff was determined retrospectively). As was noted by patients during clinical episodes, the upright tilt-induced periods of asystole would occur with little or no prodromata and produce a sudden loss of consciousness. Furthermore, the head-upright tilt test produced findings identical to those seen during spontaneous syncope in patients who later passed out while being monitored in the hospital. The second important finding was that like most patients with head-upright tilt-induced vasovagal syncope, most with prolonged asystole responded to pharmacotherapy, and a smaller number needed permanent pacemaker insertion. Furthermore, it was noted that atrioventricular sequential pacing was far superior to ventricular pacing alone in the prevention of these episodes.

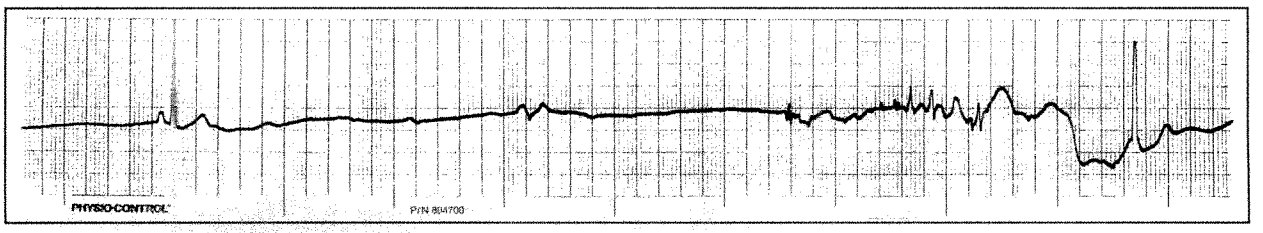


FIGURE 1. An episode of tilt-induced asystole.

The pathophysiologic mechanisms that result in vasovagal (or neurally mediated) syncope are still poorly understood. In normal subjects, assuming an upright posture results in a sudden increase in venous pooling that is usually compensated for by a reflex-controlled increase in heart rate and peripheral vasoconstriction. It is currently believed that a sudden, precipitous decrease in venous return to the heart can result in quite vigorous contractions of a nearly empty left ventricle, which in turn causes activation of a large number of afferent mechanoreceptors or C-fibers. This sudden rapid increase in afferent neural activity produces a centrally mediated paradoxic decrease in heart rate, and an increase in peripheral vasodilation, both of which result in further hypotension.[2,3,5] Recent evidence suggested that the same mechanism produces a paradoxic cerebral vasoconstriction that may also contribute to the development of syncope.[8]

Head-upright tilt-table testing has been used to provoke the aforementioned reflexes in susceptible subjects through maximal venous pooling. A number of studies demonstrated that head-upright tilt-table testing is a reasonably sensitive, specific and reproducible test for vasovagal syncope.[9-12] Furthermore, studies revealed that both heart rate and blood pressure transiently increase just before loss of consciousness.[13] Chosy and Graham[14] suggested that this reflects a transient increase in sympathetic catecholamine output just before syncope. Almquist et al[15] demonstrated that susceptibility to upright tilt-induced syncope may be facilitated by a low-level isoproterenol infusion.

Therapy: The various pharmacotherapies that were used to prevent further syncopal episodes were based on results of previous studies. β_1-adrenergic blocking agents, such as metoprolol, have been found to be effective in some patients, presumably owing to negative inotropic effects that diminish the force of ventricular contraction and thereby reduce the sudden baroreceptor activation.[15,16] Transdermal scopolamine is one of a number of vagolytic drugs that have been used to reduce the enhanced vagal tone associated with these episodes; however, there is some evidence that they may have a central action, as well.[3,13,17] Milstein et al[18] showed that disopyramide (a compound that possesses both negative inotropic and anticholinergic effects) can be effective in preventing tilt-induced syncope. Lastly, permanent pacemaker implantation has been found to be effective in some cases when severe bradycardia is unresponsive to pharmacotherapy.[3,9,19]

Milstein et al[2] suggested that pharmacotherapy may be effective in preventing further asystole episodes in these subjects, as it is in other nonasystolic patients with head-upright tilt-induced syncope. Our data suggests that this approach can be effective in many of these patients. However, as noted by Maloney et al,[3] a number of these patients may need permanent pacemaker insertion, with atrioventricular sequential pacing being more effective than ventricular pacing alone. Even permanent pacemaker placement may not totally prevent syncope, as noted in 2 of our patients. However, atrioventricular sequential pacing was effective in converting sudden "drop attacks" to periods of slowly developing hypotension with definitive prodromata that the patient can recognize. In these patients, the administration of sublingual vasoconstrictive substances (such as ergotamine tartate) appears to safely abort these episodes.

Thus, because of the severity of symptoms, the reproducible asystole seen during head-upright tilt-table testing and the tendency to need permanent pacing as therapy, we believe that these patients constitute a distinct subgroup with a disorder we have designated the malignant vasovagal syndrome.[3] The use of this term seems appropriate when one considers the actual effects of prolonged asystolic periods on cerebral function, and the potential effect of sudden severe hypotension and asystole on myocardial function and vulnerability (i.e., prolonged asystole may lower the threshold for ventricular fibrillation).[2,3,20] Milstein et al[2] and Engle[20] postulated that severe vasovagal syncope may be a potential mechanism for sudden death in some subjects, and ≥ 3 of our patients received bystander cardiopulmonary resuscitation during episodes.

As opposed to our previously reported patients,[12] these demonstrated a much greater degree of functional impairment and disability, often hampering their education and impeding them from obtaining or maintaining employment.[5] Furthermore, these recurrent sudden severe syncopal episodes place a serious psychologic burden on the patients and their families. Further studies are needed to better define this subgroup of patients with recurrent syncope and to evaluate the long-term efficacy of various therapeutic modalities.

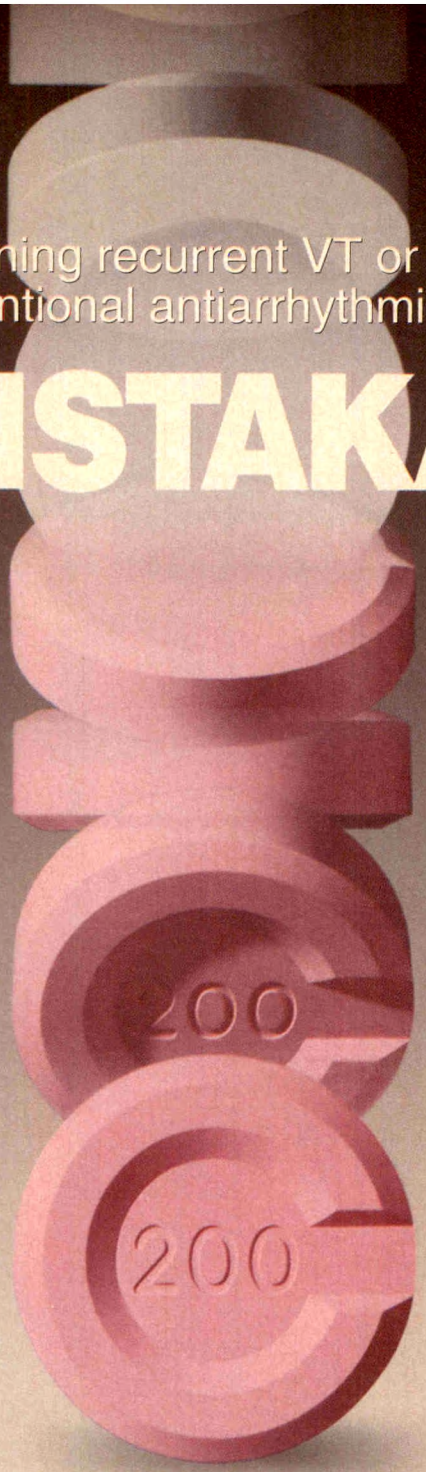
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In life-threatening recurrent VT or VF refractory to conventional antiarrhythmic agents

UNMISTAKABLY



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Cordarone® is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by serious adverse reactions.

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See adjacent page for brief summary of prescribing information.

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Cordarone® (amiodarone HCl) Tablets

BRIEF SUMMARY
(See Package Circular for full prescribing information.)

Indications and Usage: Because of life-threatening side effects and substantial management difficulties (See "Warnings" below) use only for treating documented, life-threatening recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia that are unresponsive to documented adequate doses of other antiarrhythmics or when alternative agents are not tolerated.

Controlled trials show no evidence that Cordarone favorably affects survival.

For use only by physicians familiar with and with access to (directly or via referral) all available modalities for treating recurrent life-threatening ventricular arrhythmias, including access to appropriate monitoring facilities and continuous electrocardiographic monitoring and electrophysiologic techniques. Due to the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential arrhythmia exacerbation, start Cordarone in a hospital setting.

Contraindications: Severe sinus-node dysfunction, with marked sinus bradycardia; 2nd- and 3rd-degree atrioventricular (AV) block; episodes of bradycardia which cause syncope (except when used with a pacemaker); known hypersensitivity to the drug

Warnings: Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2-5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of Cordarone is an acceptable risk, Cordarone poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using Cordarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Cordarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Cordarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when Cordarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

PULMONARY TOXICITY: Cordarone may cause a syndrome of cough and progressive dyspnea with functional, radiographic, gallium-scan and pathological data consistent with pulmonary toxicity; frequency usually varies from 2-7%, but can be as high as 10-17%. Thus, at start of therapy, perform baseline chest x-ray and pulmonary-function tests, including diffusion capacity. Repeat history, physical exam (PE), and chest x-ray every 3-6 months.

Preexisting pulmonary disease does not appear to increase risk of toxicity; however, prognosis is poorer if pulmonary toxicity develops.

Cordarone-induced pulmonary toxicity seems to result from indirect (hypersensitivity pneumonitis) or direct (interstitial/alveolar pneumonitis) toxicity.

Hypersensitivity pneumonitis usually appears early in therapy; rechallenge results in a more rapid and severe recurrence. Bronchoalveolar lavage is procedure of choice to confirm diagnosis, made when a T suppressor/cytotoxic (CD8 - positive) lymphocytosis noted. Treat with steroids and stop Cordarone.

Interstitial/alveolar pneumonitis, characterized by diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsies. Phospholipidosis (foamy cells, foamy macrophages) is present in most cases of Cordarone-induced pulmonary toxicity; however, this also occurs in approximately 50% of all Cordarone patients. Use these cells as therapy markers, not evidence of toxicity. If interstitial/alveolar pneumonitis is diagnosed, reduce dose or, preferably, withdraw Cordarone, especially if other acceptable antiarrhythmics are available. Where these measures were instituted, symptoms usually decreased in the first week; most clinical improvement was in first 2-3 weeks. Chest X-ray changes usually resolve in 2-4 months. Some experts feel steroids may be helpful. Prednisone (40-60 mg/day) or equivalent doses of other steroids have been used and tapered over several weeks. At times rechallenge at a lower dose will not result in return of toxicity. Reports suggest lower loading and maintenance doses are associated with a lower incidence of pulmonary toxicity.

In Cordarone patients, any new respiratory symptoms suggest a possibility of pulmonary toxicity; repeat and evaluate history, PE, chest X-ray, and pulmonary-function tests (with diffusion capacity). A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as decreases in diffusion capacity approach 30%, sensitivity decreases but specificity increases. A diagnostic gallium scan may also be performed.

Fatalities from pulmonary toxicity occur in about 10% of cases. However, when life-threatening arrhythmias exist, stop Cordarone (amiodarone HCl) cautiously if drug-induced pulmonary toxicity is suspected. As the most common cause of death in these patients is sudden cardiac death, first rule out other causes of respiratory impairment. Bronchoalveolar lavage or lung biopsy may be necessary to confirm the diagnosis, especially when there is no acceptable alternative therapy.

If hypersensitivity pneumonitis is diagnosed, stop Cordarone and treat with steroids. If Cordarone-induced interstitial/alveolar pneumonitis is diagnosed, start steroids and, preferably, stop Cordarone or, minimally, reduce the dose. Some cases may resolve after dose reduction and steroid use. Sometimes, rechallenge at lower doses did not result in return of interstitial/alveolar pneumonitis; however, pulmonary lesions are irreversible in some.

WORSENED ARRHYTHMIA: Cordarone may cause serious exacerbation of a presenting arrhythmia, possibly enhanced by concomitant antiarrhythmic therapy. Exacerbation (about 2-5% in most series), includes new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and Torsade de Pointes. Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients.

LIVER INJURY: Increased hepatic enzymes, mostly asymptomatic, are seen frequently. Consider discontinuation or dose reduction if increase exceeds 3 times normal, or doubles in patient with elevated baseline. Rarely, hepatic failure has been fatal.

PREGNANCY — PREGNANCY CATEGORY D. Cordarone is embryotoxic (increased fetal resorption and growth retardation) in rats at 18 times the maximum recommended oral maintenance dose. Similar results are seen in one mice strain at about 1/2 the maximum recommended maintenance dose or higher, but not in a second strain nor rabbits at doses up to 9 times the maximum recommended maintenance dose.

Neonatal hypo- or hyperthyroidism: In utero exposure can cause fetal harm. There are some reports of congenital goiter/hypothyroidism and hyperthyroidism. If used anytime during pregnancy, apprise patient of potential fetal hazard. In general, use during pregnancy only if potential benefit to the mother justifies unknown fetal risk.

Precautions

CORNEAL MICRODEPOSITS, IMPAIRMENT OF VISION: Corneal microdeposits appear in a majority of adults on Cordarone. Usually discernible only by slit-lamp, up to 10% of patients have symptoms like visual halos or blurred vision. Microdeposits are reversible if dose reduced or treatment stopped; if asymptomatic, no need to reduce dose or stop drug.

PHOTOSENSITIVITY: Seen in about 10% of patients; sun-barrier creams or protective clothing may afford some protection. On long-term therapy, may have a blue-gray skin discoloration of exposed skin. Fair complexion or excess sun exposure may increase risk; also may be related to cumulative dose and therapy duration.

THYROID ABNORMALITIES: Cordarone inhibits conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine, decreased T_3, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. Due to its release of inorganic iodine, or perhaps other reasons, Cordarone can cause either hypo- or hyperthyroidism. Monitor thyroid function before treatment and periodically thereafter, particularly in the elderly and those with history of thyroid nodules, goiter, or other thyroid dysfunction. Due to slow elimination of Cordarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for weeks or months after withdrawal.

Hypothyroidism occurred in 2-4% of patients in most series, but in 8-10% in some. To treat, reduce Cordarone dose and/or give thyroid hormone supplement. Individualize therapy, may need to stop Cordarone.

Hyperthyroidism occurs in about 2% of patients; incidence may be higher with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism is usually a greater hazard than hypothyroidism due to possible arrhythmia breakthrough or aggravation. IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Flat TSH response to TRH is confirmatory. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or Cordarone withdrawal. Antithyroid drugs, β-blockers and/or temporary steroid therapy may be needed. (See full prescribing information for additional information regarding treatment).

SURGERY: *Hypotension Postbypass:* Rarely, hypotension is seen or cessation of cardiopulmonary bypass during open-heart surgery in Cordarone patients; relationship to Cordarone is unknown.

Adult Respiratory Distress Syndrome (ARDS): Rarely, ARDS occurs in Cordarone patients after surgery. Patients usually respond to vigorous respiratory therapy; rarely, the outcome is fatal. The mechanism may be generation of superoxide radicals during oxygenation; therefore, keep operative FiO_2 as close to room air as possible.

LABORATORY TESTS: Elevated liver enzymes (SGOT and SGPT) can occur; monitor closely if high maintenance doses used. Consider dose reduction or stopping therapy if significant elevations persist or hepatomegaly occurs.

Thyroid-function tests (increased T_4 and reverse T_3, and decreased T_3) may be altered; despite these changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS: Few drug-drug interactions have been explored formally but most have shown an interaction. Thus, anticipate other interactions, especially drugs with potentially serious toxicity, like other antiarrhythmics. With its long, variable half-life, a potential for interaction also exists with drugs given after stopping Cordarone.

Digitalis: Serum digoxin increases (by up to 70%) and may reach toxic levels; onset is about 1 day. **On initiation of Cordarone, review need for digitalis and reduce its dose by about 50% or stop it.** If digitalis continued, monitor serum levels closely and observe for toxicity. Precautions probably also apply to digitoxin.

Anticoagulants: Potentiation of warfarin-type anticoagulant response is almost always seen and can result in serious or fatal bleeding. Prothrombin time may increase by 100%; onset is 3 to 4 days. **Reduce anticoagulant dose by 1/3 to 1/2, and monitor prothrombin times closely.**

Antiarrhythmic Agents: Although they have been used concurrently with Cordarone, steady-state levels of quinidine, procainamide, and phenytoin may increase during such combined therapy. Quinidine serum concentrations may increase by 33% within 2 days. Procainamide serum concentrations may increase by 55% (n-acetyl procainamide by 33%) in < 7 days. In general, reserve such combinations for patients with life-threatening ventricular arrhythmias incompletely responsive to a single agent, or incompletely responsive to Cordarone (amiodarone HCl), and start any added antiarrhythmic at a lower than usual dose with careful monitoring. During transfer to Cordarone, reduce dose of previous agents 30-50% several days after adding Cordarone, when arrhythmia suppression should be starting. After Cordarone effects are established, discontinue other antiarrhythmics if possible. If treatment is maintained, continue monitoring carefully for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias. In Cordarone patients requiring additional antiarrhythmic therapy, initial dose of such agents should be approximately 1/2 of the usual dose.

Use Cordarone cautiously with β-blockers or calcium antagonists as bradycardia, sinus arrest, and AV block may be potentiated; if necessary, Cordarone can continue after pacemaker insertion in patients with severe bradycardia or sinus arrest.

ELECTROLYTE DISTURBANCES: May be ineffective or arrhythmogenic if hypokalemia is present; correct any potassium or magnesium deficiency before starting drug.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Fertility reduced in male and female rats at 8 x the highest recommended human maintenance dose. Cordarone caused a statistically significant, dose-related increase in thyroid tumors in rats. Incidence greater than control even at lowest dose tested, i.e., about 1/2 the highest recommended human maintenance dose. Mutagenicity studies were negative.

PREGNANCY: PREGNANCY CATEGORY D — See **Warnings.**

LABOR AND DELIVERY: Occurrence of adverse effects during labor or delivery is unknown. Preclinical studies in rodents have shown no effect on gestation duration or parturition.

NURSING MOTHERS: Cordarone is excreted in human milk; breast-feeding may expose nursing infants to a significant drug dose. Nursing offspring of lactating rats given Cordarone were less viable and had reduced body-weight gains. Advise mothers to discontinue nursing before taking.

PEDIATRIC USE: Safety and effectiveness have not been established.

Adverse Reactions: Adverse effects are very common (about 3/4 of all patients) with doses of 400 mg/day or more, and cause 7-18% to discontinue. The most serious are pulmonary toxicity, arrhythmia exacerbation, and rare serious liver injury (see "**Warnings**"), but other adverse effects constitute important problems. They are often reversible by reducing dose and virtually always reversible by stopping Cordarone. Most adverse effects appear more frequent with continued treatment beyond 6 months; rates appear relatively constant beyond one year. Neurologic problems, including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy are common (20-40% of patients); these may respond to dose reduction, rarely need to stop therapy.

Gastrointestinal (GI) complaints, commonly seen with high doses (i.e., loading dose), usually respond to dose reduction or divided doses; rarely need to stop drug.

Asymptomatic corneal microdeposits. See **Precautions** and full prescribing information.

Photosensitivity. See **Precautions** and full prescribing information.

Cardiovascular adverse reactions, other than arrhythmia exacerbation, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dose reduction but may require a pacemaker. CHF rarely requires stopping drug. Cardiac conduction abnormalities occur infrequently and are reversible upon stopping drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

Each reported in 10-33% of patients: GI—Nausea and vomiting.

Each reported in 4-9% of patients: Dermatologic—Solar dermatitis/photosensitivity. Neurologic—Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias; GI—Constipation, anorexia; Ophthalmologic—Visual disturbances; Hepatic—Abnormal liver-function tests; Respiratory—Pulmonary inflammation or fibrosis.

Each reported in 1-3% of patients: Thyroid—Hypo- or hyperthyroidism; Neurologic—Decreased libido, insomnia, headache, sleep disturbances; Cardiovascular—CHF, cardiac arrhythmias, SA node dysfunction; GI—Abdominal pain; Hepatic—Nonspecific hepatic disorders; Other—Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

Each reported in < 1% of patients: Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities. Rarely hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia.

Adverse reactions most frequently requiring Cordarone discontinuation include pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, CHF, and elevated liver enzymes. Symptoms causing discontinuation less often include visual disturbances, solar dermatitis, blue skin discoloration, hyper- or hypothyroidism.

Overdosage: The few reports of Cordarone overdose, in which 3 to 8 grams were taken, resulted in no deaths or permanent sequelae. Animal studies indicate that Cordarone has a high oral LD_{50} (>3,000 mg/kg).

Along with general supportive measures, monitor patient's cardiac rhythm and blood pressure; if bradycardia ensues, may use a β-adrenergic agonist or pacemaker. Use positive inotropic and/or vasopressor agents to treat hypotension with inadequate tissue perfusion. Neither Cordarone nor its metabolite is dialyzable.

Dosage and Administration: See full prescribing information.

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Usefulness of Predischarge Electrophysiologic Study in Predicting Late Outcome After Surgical Ablation of the Accessory Pathway in the Wolff-Parkinson-White Syndrome

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A predischarge electrophysiologic study was performed in 113 patients with the Wolff-Parkinson-White (WPW) syndrome who had undergone surgical ablation of the accessory pathway. The study was performed 5 to 20 (mean 10 ± 3) days after surgery. There were 82 male and 31 female patients (aged 4 to 58 years, mean 36 ± 13). Sixty-one patients (54%) had manifest, 52 (46%) had concealed and 12 (11%) had multiple accessory pathways. All but 1 patient had atrioventricular reentrant tachycardia incorporating single or multiple accessory pathways during the control electrophysiologic study. The accessory pathways were located in the left ventricular free wall in 60% of cases, right ventricular free wall in 22%, posteroseptum in 13%, and anteroseptum in 5%. The predischarge electrophysiologic study showed that the accessory pathway was capable of anterograde and retrograde conductions in 4 patients (all with manifest WPW syndrome). Four patients showed induction of supraventricular tachycardia, including 2 with atrioventricular reentrant tachycardia, and 2 with atrioventricular nodal reentrant tachycardia. Recurrence of supraventricular tachycardia was noted in 5 patients during a follow-up of 28 ± 26 months. Of these 5 patients, 2 had inducible and 3 had no inducible supraventricular tachycardia during the predischarge electrophysiologic study. Thus, the predischarge electrophysiologic study could predict late outcome with recurrence of preexcitation or supraventricular tachycardia in patients who had undergone surgical ablation of the accessory pathway with an overall predictive accuracy of 95% (107 of 113 patients), negative predictive value of 96% (103 of 107), and positive predictive value of 67% (4 of 6).

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Surgical ablation of the accessory pathway provides a cure for symptomatic patients with the Wolff-Parkinson-White (WPW) syndrome.[1–13] It can achieve a high success rate with low mortality and morbidity in institutions with extensive experience in this procedure. Long-term follow-up data regarding the outcome of patients who underwent this procedure are scanty. Fischell et al[11] reported that 98% of 45 consecutive patients with the WPW syndrome who had undergone surgical ablation of the accessory pathway were free of preexcitation-related arrhythmias over a mean follow-up of 3.1 years. Davis et al[12] reported a 6-month success rate of 92% after surgery on 214 accessory pathways in 174 patients. Success was determined by a late, 6-month postoperative electrophysiologic study. In this report, we evaluate the long-term outcome of surgery and assess the value of the predischarge electrophysiologic study in predicting the late outcome of patients undergoing surgical ablation of the accessory pathway.

METHODS

Patients: From December 1980 to February 1991, 123 patients with the WPW syndrome underwent surgical ablation of the accessory pathway, because of recurrent symptomatic tachyarrhythmias. A predischarge electrophysiologic study was performed in 113 patients (82 men and 31 women, age range 4 to 58 years mean 36 ± 13) who consented to the procedure. Sixty-one patients (54%) had manifest and 52 (46%) had concealed WPW syndrome. All 113 patients had multiple electrocardiographic documentation of tachyarrhythmias, including supraventricular tachycardia in 80, atrial fibrillation in 24, and atrial fibrillation and supraventricular tachycardia in the remaining 9. Organic heart disease was present in 12 patients. All but 1 patient had induction of atrioventricular reentrant tachycardia incorporating the accessory pathway for retrograde conduction. Twelve patients (11%) had multiple accessory pathways, so that a total of 126 accessory pathways were operated on. The accessory pathways were located in the left ventricular free wall in 60% of cases, right ventricular free wall in 22%, posteroseptum in 13%, and anteroseptum in 5%.

Electrophysiologic study and surgical ablation: All 113 patients had a preoperative electrophysiologic study to confirm the diagnosis of the WPW syndrome, determine the location of the accessory pathway, identify the presence of multiple accessory pathways, and evaluate the mechanisms of the tachyarrhythmias. Details of the

electrophysiologic study protocol were described previously.[14] Epicardial mapping was performed using a handheld electrode probe after exposure of the heart through a median sternotomy. The site of the earliest ventricular activation was verified during sinus rhythm or atrial pacing; the site of the earliest atrial activation was verified during ventricular pacing or atrioventricular reentrant tachycardia. The surgical technique used in this series was the endocardial approach described by Gallagher, Sealy and their coworkers.[1-4] After completion of surgical dissection of the accessory pathway, a repeat electrophysiologic study was performed to ensure the success of surgery. The predischarge electrophysiologic study was performed 5 to 20 days (mean 10 ± 3) after surgery while the patient was on no antiarrythmic drugs.

Surgical dissection as evaluated by predischarge electrophysiologic study was considered to be successful when there was no accessory pathway conduction in both the anterograde and retrograde directions, and when there was no induction of supraventricular tachycardia. It was considered to be unsuccessful when accessory pathway conduction was present in either the anterograde or retrograde direction, or when there was induction of either atrioventricular reentrant or nodal reentrant tachycardia. All 113 patients were followed up in the clinic with multiple recordings of electrocardiograms at rest, 24-hour Holter monitoring and treadmill exercise testing. Mean follow-up duration was 28 ± 26 months. A diagnosis of late failure was obtained when ventricular preexcitation or supraventricular tachycardia was documented electrocardiographically.

Data were expressed as mean ± SD and were analyzed using the Student *t* test for paired data. Sensitivity, specificity, positive and negative predictive values, and total predictive accuracy were calculated using the predischarge electrophysiologic study as the reference, and the emergence of ventricular preexcitation or electrocardiographic documentation of supraventricular tachycardia as the standard for late failure. They were defined as follows:

$$\text{Sensitivity} = \frac{\text{true positives}}{\text{true positives} + \text{false negatives}}$$

$$\text{Specificity} = \frac{\text{true negatives}}{\text{true negatives} + \text{false positives}}$$

$$\text{Positive predictive value} = \frac{\text{true positives}}{\text{true positives} + \text{false positives}}$$

$$\text{Negative predictive value} = \frac{\text{true negatives}}{\text{true negatives} + \text{false negatives}}$$

$$\text{Total predictive accuracy} = \frac{\text{true positives} + \text{true negatives}}{\text{all positives} + \text{all negatives}}$$

RESULTS

Conduction properties and induction of tachycardia (Table I): Ventricular preexcitation was noted in 4 patients during the predischarge electrophysiologic study. The longest atrial paced cycle lengths before surgery that produced second-degree accessory pathway block were 200, 280, 330 and 300 ms, respectively, and after surgery 280, 260, 400, and 260 ms, respectively. The longest atrial paced cycle length that produced second-degree atrioventricular nodal block could be compared in 67 patients before and after surgery (311 ± 41 ms before and 308 ± 65 ms after surgery (p = not significant). The effective refractory period of the atrioventricular node could be measured in 27 patients before and after surgery (297 ± 50 ms before and 286 ± 75 ms after; p = not significant).

Intact retrograde accessory pathway conduction was noted in 4 patients during the predischarge electrophysiologic study. All 4 patients had intact anterograde accessory pathway conduction with ventricular preexcitation. The longest ventricular paced cycle lengths that produced second-degree ventriculoatrial block in the accessory pathway were <280, <300, 360 and 280 ms, respectively, before surgery, and <280, <280, 360 and <280 ms, respectively, after surgery. Intact retrograde normal pathway conduction was noted in 63 patients, and absence of retrograde conduction was noted in the remaining 46. Two patients had induction of atrioventricular reentrant tachycardia; both had intact anterograde and retrograde accessory pathway conductions. One patient had induction of sustained fast-slow form atrioventricular nodal reentrant tachycardia, and 1 had induction of nonsustained slow-fast form atrioventricular nodal reentrant tachycardia. Fourteen patients had induction of fast-slow form atrioventricular nodal reentrant echoes (<5 beats), and 2 had induction of 1 slow-fast form atrioventricular nodal reentrant echo. The remaining 93 patients had no induction of atrioventricular or atrioventricular nodal reentrant echoes or tachycardia.

Prediction of late outcome (Table II): Of the 107 patients with surgical success as defined by the predischarge electrophysiologic study, 3 had late electrocardiographic documentation of supraventricular tachycardia, and 1 had ventricular preexcitation. The other 103 patients were free of symptoms and had no ventricular preexcitation. Of the 6 patients with surgical failure as defined by the predischarge electrophysiologic study, 4 continued to have ventricular preexcitation, but only 2 of these had documented supraventricular tachycardia. The other 2 patients without ventricular preexcitation, but with induction of atrioventricular nodal reentrant tachycardia had no documented supraventricular tachycardia during follow-up. Thus, sensitivity of the predischarge electrophysiologic study in predicting late outcome was 50%, whereas specificity was 98%. Positive predictive value was 67%, negative predictive value 96% and total predictive accuracy was 95%.

DISCUSSION

Assessment of surgical outcome: The immediate outcome of surgery is usually evaluated using an intraoperative electrophysiologic study at the completion of the operation. If either anterograde or retrograde accessory pathway conduction is present, the surgery is repeated until the accessory pathway is no longer conducting. However, the intraoperative electrophysiologic study can be misleading, because acute traumatic edema, the cardioplegic solution and anesthetic agents can transiently suppress rather than permanently interrupt

accessory pathway conduction. The predischarge electrophysiologic study has been used widely in assessing surgical outcome in the WPW syndrome. However, data concerning its value in predicting late outcome are limited.[11-13,15,16] Fischell et al[11] operated on 46 accessory pathways in 45 consecutive patients who had an electrophysiologic study 2 to 7 days after surgery. One patient had accessory pathway conduction with inducible atrioventricular reentrant tachycardia, and another had inducible atrioventricular nodal reentrant tachycardia. By actuarial analysis, 3 years after surgery, 98% of patients were free of preexcitation-related arrhythmias. Davis et al[12] compared the value of serial 12-lead electrocardiograms, telemetric monitoring of the electrocardiogram, and the predischarge electrophysiologic study performed 1 week after surgery in predicting the 6-month outcome of surgery. They reported sensitivity, specificity and accuracy of the predischarge electrophysiologic study to be 10, 99 and 92%, respectively, in predicting the outcome of the electrophysiologic study 6 months after surgery. They concluded that the late electrophysiologic study is the most accurate method of assessing surgery for supraventricular tachycardia. They downgraded the value of serial electrocardiograms and the predischarge electrophysiologic study, because sensitivity was only 60%, even though specificity and accuracy were 99 and 96%, respectively.

Value of various assessments in predicting outcome: All patients in this series were considered a surgical success as defined by the intraoperative electrophysiologic study in which there was no evidence of accessory pathway conduction at the completion of surgery. Accessory pathway conduction had returned by the time of the predischarge electrophysiologic study in 4 patients. Thus, the accuracy of the intraoperative electrophysiologic study in predicting the short-term outcome of accessory pathway ablation was 96%. The sensitivity, specificity and total predictive accuracy of the predischarge electrophysiologic study in predicting long-term outcome in this series were 50, 98 and 95%, respectively. These data are similar to those of Davis et al.[12] Both series showed that the predischarge electrophysiologic study was not sensitive in predicting long-term surgical failure, but was highly specific and very accurate. This is understandable from Bayes' theorem that states that a high surgical success provides for a low pretest prevalence of surgical failure in the sample, rendering the sensitivity of the test low. However, this study used electrocardiographic ventricular preexcitation or documentation of supraventricular tachycardia as evidence of surgical failure during follow-up, whereas Davis et al[12] used a late 6-month electrophysiologic study as the standard. It should be noted that all patients in this series were operated on for recurrent and troublesome symptomatic tachyarrhythmias needing multiple hospital visits for treatment, and had multiple electrocardiographic documentation of tachyarrhythmias before surgery. It is very unlikely that the same arrhythmias would not have been documented if they recurred during follow-up.

The induction of nonclinical arrhythmias during the predischarge electrophysiologic study needs some comment. Sixteen of the 113 patients had induction of atrioventricular nodal reentrant echoes, and 2 had induction of atrioventricular nodal reentrant tachycardias. However, no patient had symptomatic arrhythmias during follow-up. Fischell et al[11] noted induction of atrioventricular nodal reentrant tachycardia in 1 of 45 patients with the WPW syndrome during the predischarge electrophysiologic study after surgery. That patient had no supraventricular tachycardia during later follow-up. Reyes et al[13] noted induction of atrioventricular nodal reentrant echoes in 5 patients, and atrioventricular nodal reentrant tachycardia in 2 during an electrophysiologic study after surgery in 62 undergoing surgical ablation of accessory pathways. Only the 2 patients with induction of atrioventricular nodal reentrant tachycardia had a late occurrence of supraventricular tachycardia during follow-up. Thus, induction of atrioventricular nodal reentrant echoes alone are probably not significant, whereas that of atrioventricular nodal reentrant tachycardia may predict a late occurrence of tachycardia.

Clinical implications: This study demonstrates that the predischarge electrophysiologic study accurately predicts the late outcome of patients undergoing accessory pathway ablation. However, this study also demonstrates that when accessory pathway ablation can be ensured by the intraoperative electrophysiologic study at the completion of surgery, both the early and late electrophysiologic studies are unnecessary, because the yields are low. Indications for an electrophysiologic study in patients after surgery with the WPW syndrome undergoing accessory pathway ablation should be similar to those before surgery.

TABLE I Findings During the Predischarge Electrophysiologic Study

Conduction Properties	No. of Pts.
Anterograde conduction	
Presence of ventricular preexcitation	4
Retrograde conduction	
Intact accessory pathway conduction	4
No induction of echoes	2
Atrioventricular reentrant tachycardia	2
Intact normal pathway conduction	63
No induction of echoes	45
Fast-slow atrioventricular nodal reentrant echoes	14
Slow-fast atrioventricular nodal reentrant echoes	2
Atrioventricular nodal reentrant tachycardia	2
No ventriculoatrial conduction	46

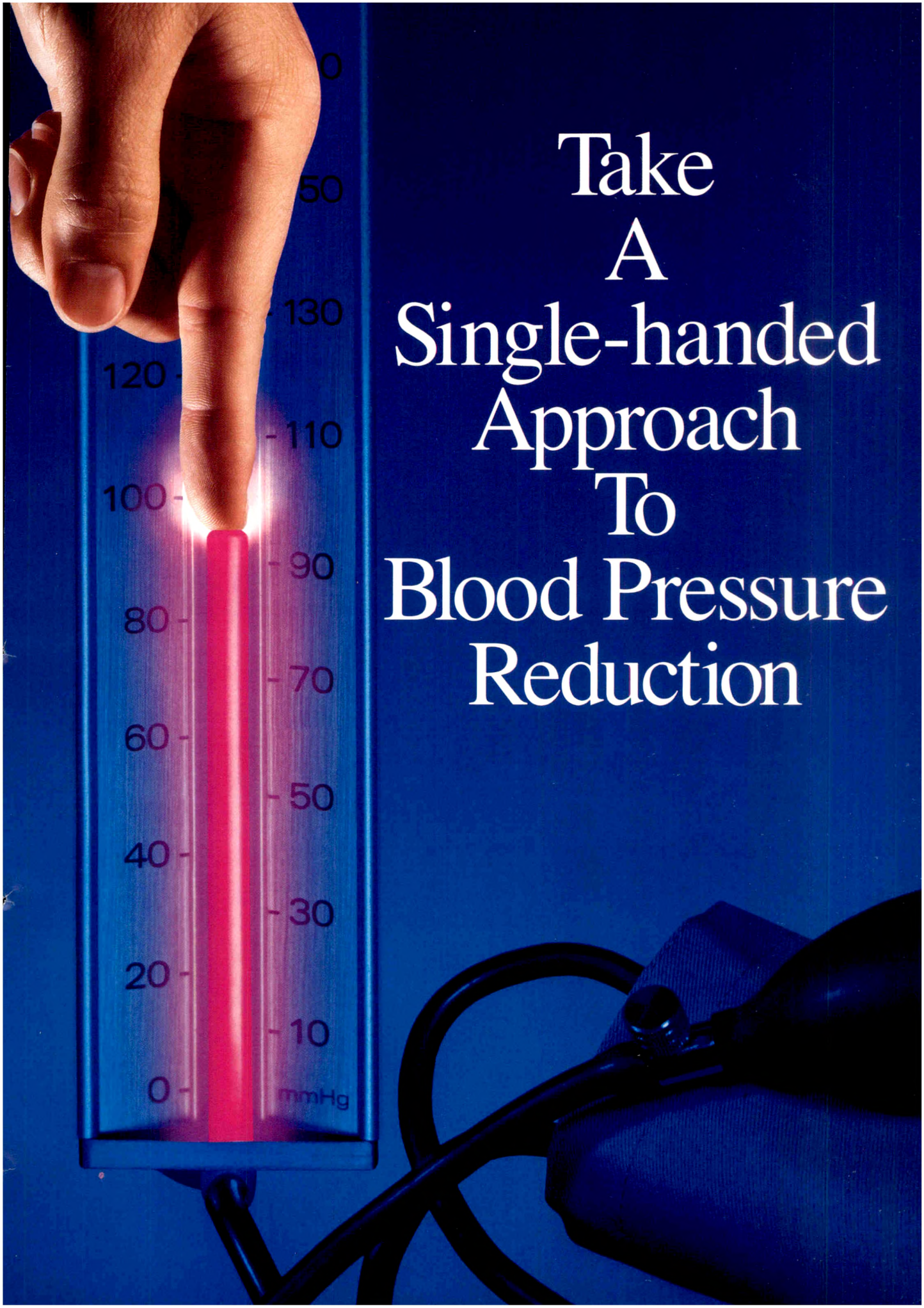
TABLE II Sensitivity, Specificity and Predictive Accuracy of the Predischarge Electrophysiologic Study in Predicting Late Outcome

Sensitivity	50% (4/8)
Specificity	98% (103/105)
Positive predictive value	67% (4/6)
Negative predictive value	96% (103/107)
Total predictive accuracy	95% (107/113)

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INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m², respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

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Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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As key members of the health care team, nurses *can* make a difference in helping to curb drug abuse, and in preventing some of its deadliest consequences. The next time you suspect a patient may be using cocaine—or *any* illegal substance—have a heart-to-heart talk about the damage these drugs can do.

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Significance of Ventricular Arrhythmias in Systemic Hypertension with Left Ventricular Hypertrophy

Stuart D. Pringle, MD, Francis G. Dunn, MB ChB, Peter W. Macfarlane, PhD, James H. McKillop, PhD, A. Ross Lorimer, MD, and Stuart M. Cobbe, MD

Hypertensive patients with the electrocardiographic (ECG) pattern of left ventricular (LV) hypertrophy and strain are at increased risk of sudden death. It has been suggested that ventricular arrhythmias may be responsible. The prevalence and significance of ventricular arrhythmias was therefore studied in 90 hypertensive patients with LV hypertrophy and strain by undertaking 48-hour ambulatory ECG monitoring, ECG signal-averaging and programmed ventricular stimulation.

Complex ventricular ectopic activity (Lown grade ≥3) was detected in 59 patients (66%). Eleven patients (12%) had episodes of nonsustained ventricular tachycardia. There were no sustained arrhythmias either on ambulatory ECG monitoring or induced by programmed ventricular stimulation. Only 1 patient had ventricular late potentials recorded by the signal-averaged electrocardiogram. Therefore, there was little to suggest an underlying arrhythmogenic substrate in these patients. In conclusion, whereas ventricular arrhythmias occur often in patients with LV hypertrophy associated with systemic hypertension, their significance, if any, remains to be established.

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In the Framingham Study, hypertensive patients with electrocardiographic (ECG) left ventricular (LV) hypertrophy were at increased risk of premature cardiovascular death.[1] The fact that the majority of these deaths were sudden (i.e., within 1 hour from the onset of symptoms)[2] has led to the theory that ventricular arrhythmias may be responsible. Certainly, patients with LV hypertrophy have an increased frequency of complex ventricular ectopic beats[3] and nonsustained ventricular tachycardia.[4,5] Although these studies have demonstrated an association between ventricular arrhythmias and hypertensive LV hypertrophy, the pathologic significance of these arrhythmias has not been clarified. In particular, whether these arrhythmias are benign or are causally related to sudden death remains to be established. It is therefore important to determine whether hypertensive LV hypertrophy provides a genuine arrhythmogenic substrate.

The aim of this study was (1) to determine the prevalence of ventricular arrhythmias in a large series of patients with hypertensive LV hypertrophy and, (2) to evaluate their significance by investigating the potential for a reentry substrate through studying the signal-averaged electrocardiogram and undertaking invasive electrophysiologic studies.

METHODS

Patients: Patients with essential hypertension and ECG LV hypertrophy and strain were identified from the blood pressure clinic database and invited to participate. Those who agreed were recruited consecutively. The study group consisted of 90 patients (68 men and 22 women, mean age 57 years [range 25 to 79]) (Table I). Secondary hypertension was excluded by clinical evaluation, routine biochemical screening, chest x-ray and, in most cases, by previous intravenous pyelography.

Electrocardiography: To ensure uniformity all the 12-lead electrocardiograms were recorded using computer-based methods developed locally.[6] For the purposes of this study, LV hypertrophy and strain were defined as being present when there was ST depression of ≥0.05 mV and T-wave inversion of ≥0.1 mV in leads I, aVL and V_5 or V_6 in the presence of voltage criteria (SV1 + RV5 >3.5 mV) for LV hypertrophy. These are not the criteria used by the computer program but were selected for comparative reasons with the knowledge that the presence of LV hypertrophy was confirmed by echocardiography.

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TABLE I Clinical Characteristics of Patients

Age (yr)	57 (range 25–79)
Men:women	68:22
Angina pectoris	9
Previous myocardial infarction	5
Systolic blood pressure (mm Hg)	155 (28)
Diastolic blood pressure (mm Hg)	89 (15)
Hypertension duration (yr)	7.4 (8.0)
Drug therapy	
Thiazides (no. [%])	34 (38)
β blockers (no. [%])	38 (42)
Ca antagonists (no. [%])	40 (44)
Angiotensin-converting enzyme inhibitors (no. [%])	23 (25)
Mean no. of drugs	2.51 (1.4)
Potassium (mmol/liter)	4.16 (0.42)
Magnesium (mmol/liter)	0.81 (0.10)
LV mass index (g/m^2)	196.4 (50.5)

Results are expressed as mean ± 1 SD unless otherwise stated.
Ca = calcium; LV = left ventricular.

TABLE II Prevalence of Ventricular Arrhythmias

	Ventricular Ectopic Beats Per Hour						Nonsustained Ventricular Tachycardia
	<10	10–30		>30	Couplets		
No. of pts.	70	8		12	25		11
Lown grade	0	1	2	3	4a	4b	5
No. of pts.	3	28	0	15	4	4	36

Echocardiography: The degree of LV hypertrophy was assessed by echocardiography performed with an Advanced Technology Laboratories Ultramark 8 mechanical scanner using a 3 MHz transducer. LV mass was calculated by an anatomically validated method.[7]

Ambulatory electrocardiographic monitoring: Forty-eight-hour ambulatory ECG monitoring was undertaken with an Oxford Medilog II FM recorder during each patient's normal activities. The tapes were analyzed by an experienced technician using a Reynolds Pathfinder high-speed analyzer interfaced to a PDP8A minicomputer.[8] Verification was achieved by visual inspection of the monitor during playback of the tapes and examination of the ECG printouts. Manual backup has been shown to improve the reproducibility of computer-assisted techniques.[9]

Ventricular ectopic activity was classified according to Lown's grading.[10] Nonsustained ventricular tachycardia was defined as ≥3 consecutive ventricular ectopic complexes occurring at a rate of >120 beats/min.

Signal-averaged electrocardiogram: The signal-averaged electrocardiograms were recorded with an Arrhythmia Research Technology 101 system with the patient supine. The normal range was defined by combining the most discriminatory features from several previous reports.[11–15] Normal values were a filtered QRS duration of ≤114 ms, a duration of low-amplitude signals <40 uV ≤38 ms, a root-mean-square amplitude in the last 40 ms of filtered QRS of ≥25 uV.

In addition to these automatic measurements, late potentials were defined as being present if, after the QRS complex, potentials were visible with an amplitude >3 times the baseline noise.

Electrophysiologic study: The desirability of performing electrophysiologic studies was considered for each patient bearing in mind their age, general health and co-existent medical problems. For logistic and ethical reasons, it was not possible for all patients to have an electrophysiologic study performed but it was considered important to include patients both with and without ventricular arrhythmias detected noninvasively. In practice, 62 patients were considered to be suitable and 24 agreed to undergo electrophysiologic testing. The remaining 38 patients declined mainly because of a reluctance to be admitted to the hospital rather than anxiety about the procedure.

Programmed ventricular stimulation was performed with a quadripolar pacing catheter, introduced under local anaesthesia, using first single (S2) and then double extrastimuli (S2 + S3) at the right ventricular apex and outflow tract. The extrastimuli were introduced after every 8-paced beat (S1), with cycle lengths of 600 and 450 ms. The extrastimuli were begun 400 ms after the last S1 and the interval then reduced in 10 ms stages until a sustained ventricular arrhythmia was induced or until the extrastimulus failed to capture (i.e., the effective refractory period was reached). If no arrhythmia was induced with single extrastimuli, the same procedure was repeated with double extrastimuli. The end point of the protocol was sustained monomorphic ventricular tachycardia lasting 30 seconds or requiring immediate termination, ventricular fibrillation, or completion of the protocol at both pacing sites and both cycle lengths.

Statistical methods: When the 2 groups of data were compared, a 2-sample *t* test was used if the data were normally distributed, and when the distribution was skewed, the nonparametric Mann-Whitney U test was used. A 5% significance level was used to determine differences.[16]

Ethical approval: The study was approved by the hospital ethical committee. The patients provided written informed consent for the invasive procedures and verbal consent for the noninvasive investigations.

RESULTS

Results are expressed as the number of patients followed by the percentage in parentheses.

Ambulatory electrocardiographic monitoring: ISOLATED VENTRICULAR ECTOPIC BEATS: Twelve patients (13%) had >30 ventricular ectopic beats per hour, 8 (9%) had between 10 and 29 ventricular ectopic beats per hour, a further 67 patients (74%) had <10 ventricular ectopic beats per hour and only 3 patients (3%) had no ventricular ectopic beats detected during the 48-hour period (Table II).

COMPLEX VENTRICULAR ECTOPIC BEATS AND COUPLETS: Forty-nine patients (54%) had multiform ectopic beats, 25 (28%) had couplets and 36 (40%) had early (R-on-T) ectopic beats.

NONSUSTAINED VENTRICULAR TACHYCARDIA (TABLES II AND III): Eleven patients (12%) had at least 1 episode of nonsustained ventricular tachycardia. In 6 patients this

was a single episode, 3 had 2 episodes, 1 had 4 episodes, and 1 patient had 10 episodes. Of these 26 episodes, 20 were triplets and 6 were >3 beats. The longest run was 9 beats. In no patient were these episodes associated with symptoms recorded on the diary cards. Three patients with nonsustained ventricular tachycardia also had >30 ectopic beats per hour. The mean number of ectopic beats tended to be greater in patients with nonsustained ventricular tachycardia than in those without (863 ± 1,850 vs 345 ± 890). However, because of the large standard deviations, this difference was not statistically significant.

LOWN GRADING: The distribution of patients by their maximal Lown grade of ectopic beats was as follows (Table II): grade 0, 3 (3%); grade 1, 28 (31%); grade 2, 0; grade 3, 15 (17%); grade 4a, 4 (4%); grade 4b, 4 (4%); and grade 5, 36 (40%).

Signal-averaged electrocardiogram: The signal-averaged electrocardiogram was technically satisfactory in 88 patients: 23 (26%) patients had a prolonged QRS duration, 3 had a decreased root-mean-square voltage, and 1 patient had prolonged duration of low-amplitude signals. In terms of fulfilling the criteria for late potentials, 2 patients met 2 criteria and only 1 patient fulfilled all 3 criteria. This latter patient was the only one to have visible late potentials.

Electrophysiologic testing: There were no inducible sustained ventricular arrhythmias. Seven patients had short episodes of nonsustained polymorphic ventricular tachycardia with a maximal duration of 13 beats. There was no apparent relation between nonsustained ventricular tachycardia detected on Holter monitoring and that induced by ventricular stimulation. Seven of the patients with Holter nonsustained ventricular tachycardia underwent electrophysiologic testing: 3 had inducible nonsustained ventricular tachycardia and 4 did not. Of the 17 who did not have nonsustained ventricular tachycardia on Holter, 4 had inducible nonsustained ventricular tachycardia and 13 did not. There were no differences in the effective refractory period or HV interval in those with or without induced nonsustained ventricular tachycardia.

Comparison of patients with and without nonsustained ventricular tachycardia detected on Holter monitoring: There were no significant differences in age, basal blood pressure, duration of hypertension, LV mass index, serum potassium, serum magnesium or drug therapy in patients with nonsustained ventricular tachycardia compared with those without nonsustained ventricular tachycardia detected on Holter monitoring (Table III). The electrocardiogram, signal-averaged electrocardiogram and electrophysiologic measurements were also similar in the 2 groups.

TABLE III Comparison of Age, Blood Pressure, Potassium, Magnesium, Left Ventricular Mass and Drug Therapy in Patients With and Without Nonsustained Ventricular Tachycardia

Nonsustained Ventricular Tachycardia	Present (n = 11)	Absent (n = 79)
Age (yr)	58 (11)	57 (11)
Systolic blood pressure (mm Hg)	149 (31)	155 (27)
Diastolic blood pressure (mm Hg)	92 (17)	89 (14)
Hypertension duration (yr)	8.4 (10.0)	7.2 (7.8)
LV mass index (g/m^2)	203 (42.6)	196 (52.0)
Potassium (mmol/liter)	4.2 (0.48)	4.2 (0.42)
Magnesium (mmol/liter)	0.84 (0.06)	0.81 (0.10)
Drug therapy		
Thiazides (no. [%])	5 (45)	29 (37)
β blockers (no. [%])	6 (55)	32 (41)
Ca antagonists (no. [%])	4 (36)	36 (46)
Angiotensin-converting enzyme inhibitors (no. [%])	2 (18)	21 (27)
Mean no. of drugs	2.2 (1.3)	2.6 (1.4)

Results are expressed as mean ± 1 SD unless otherwise stated. There were no significant differences.
Abbreviations as in Table I.

DISCUSSION

Prevalence of ventricular arrhythmias: The hypothesis that ventricular arrhythmias may be important in hypertensive heart disease was suggested initially by epidemiologic data showing that hypertensive patients with LV hypertrophy were at increased risk of sudden death compared with hypertensive patients without LV hypertrophy.[1,2,17] Furthermore, patients with hypertensive LV hypertrophy have an increased frequency of complex ventricular ectopic beats[3] and nonsustained ventricular tachycardia.[4,5] Although these studies have demonstrated an association between ventricular arrhythmias and hypertensive LV hypertrophy, whether these arrhythmias are benign or are causally related to sudden death remains to be established. Therefore, the aim of this study was to examine the pathologic significance of these arrhythmias.

In the present study, simple and complex ventricular ectopic beats occurred often in patients with hypertensive LV hypertrophy. Their prevalence was similar to previous studies of patients with hypertrophic cardiomyopathy,[18] aortic valve disease[19] and hypertensive LV hypertrophy.[3,20,21] Nonsustained ventricular tachycardia occurred in 12% of the patients. This is also in keeping with the results of most other studies of hypertensive patients with reported prevalences of 10% (6 of 61),[22] 15% (29 of 196),[23] 17% (3 of 18)[20] and 28% (14 of 50).[4]

Thiazide diuretics may increase and β blockers may decrease ventricular arrhythmias. Although there were no significant differences in treatment between the groups (Table III), we cannot exclude an effect from continuing drug therapy based on the prevalence of ventricular arrhythmias. Coronary arteriography was performed in 35 and thallium perfusion scintigraphy in 80 of these patients. There was no relation between silent or symptomatic ischemia and ventricular arrhythmias.

Significance of ventricular arrhythmias: More important than simply the prevalence of complex ventricular ectopic beats is their significance in terms of providing a genuine arrhythmogenic substrate. There are no reports of hypertensive LV hypertrophy causing sustained ventricular tachycardia; all reports are of triplets or runs of nonsustained ventricular tachycardia with a median duration of 7 beats. Nor have there been studies examining the relation between ventricular ectopic beats detected on ambulatory ECG monitoring and prognosis in hypertensive patients with LV hypertrophy.

Two studies, however, have examined the influence of ventricular ectopic beats detected on short ECG recordings in general population samples that included patients with hypertension and LV hypertrophy.[17,25] Ventricular ectopic beats alone were associated with only a modest increase in risk of sudden death (2.2-fold).[25] Although ventricular ectopic beats on 12-lead electrocardiograms in the Framingham Study were associated with an increased risk of sudden death,[17] they were not predictive independently of other ECG abnormalities.[26]

The published data concerning ventricular arrhythmias as independent predictors for sudden death has recently been reviewed.[27] In patients without heart disease or with heart disease and normal LV function, there is little evidence to support the hypothesis that simple or complex arrhythmias including short runs of nonsustained ventricular tachycardia are associated with increased risk of sudden death.

For these reasons it was considered important in the present study to assess whether an arrhythmogenic substrate exists in patients with hypertensive LV hypertrophy.

Evidence for an arrhythmogenic substrate? In contrast to the findings of increased ectopic activity in these patients, there was little evidence of an underlying arrhythmogenic substrate. There were no inducible arrhythmias on electrophysiologic testing in 24 patients and only 1 patient had ventricular late potentials on the signal-averaged electrocardiogram. The argument might be put forward that by performing electrophysiologic studies in only one fourth of the patients, it is not possible to comment on the group as a whole. This was the reason for recording the signal-averaged electrocardiogram in all patients. Evidence is accumulating that the signal-averaged electrocardiogram is extremely useful in predicting the inducibility of ventricular tachycardia by electrophysiologic testing in patients with syncope of unknown origin,[13] in patients with nonsustained ventricular tachycardia,[15] and in patients with sustained ventricular tachycardia or previous cardiac arrest.[14] The chief advantage of the signal-averaged electrocardiogram in the context of the present study is the excellent negative predictive accuracy of approximately 90%.[15] Thus, the absence of late potentials in most hypertensive patients in this study adds considerable weight to the negative findings of the electrophysiologic studies.

There have been 2 other reports of programmed ventricular stimulation in patients with hypertensive LV hypertrophy.[27,28] In these studies the patients underwent electrophysiologic testing as part of the routine investigation of suspected heart disease or unexplained syncope, whereas the patients in the present report were selected purely for this study. Nonsustained ventricular tachycardia was induced in 25% (3 of 12)[27] and in 29% (4 of 14)[28] of patients in the previous reports and in 29% (7 of 24) of patients in the present study. Sustained ventricular tachycardia was not inducible in 1 study,[27] and in the other study was inducible in only 2 patients, both of whom had cardiac decompensation.[28] Unfortunately it was not stated whether this was a monomorphic or polymorphic tachycardia. It is questionable whether the induction of polymorphic ventricular tachycardia during electrophysiologic testing is a clinically relevant finding or a nonspecific response to ventricular premature stimuli.[29] Sustained monomorphic ventricular tachycardia, which is more likely to be a clinical rhythm, was not induced in either of these studies or in the present study. Another consideration was whether a more aggressive protocol using triple extrastimuli should have been used in this study. The increased sensitivity of using triple extrastimuli would risk inducing nonclinical rhythms.[29,30] Furthermore, the signal-averaged ECG results in this study reinforce the negative electrophysiologic studies.

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Comparative Effects of Fenoldopam Mesylate and Nitroprusside on Left Ventricular Performance in Severe Systemic Hypertension

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To compare the effects of fenoldopam (n = 15), a selective dopamine-1 agonist, and nitroprusside (n = 14) on left ventricular (LV) function in severely hypertensive subjects (diastolic blood pressure (BP) >120 mm Hg), both agents were infused to reduce diastolic BP by 40 mm Hg (or <110 mm Hg). Indexes of LV systolic and diastolic functions were obtained using gated radionuclide angiography before the initiation of treatment and after targeted BP was achieved. Both fenoldopam and nitroprusside effectively reduced systolic and diastolic BP to target levels. Changes in heart rate, peak filling rate and relative end-diastolic volume were similar with both agents. Baseline ejection fraction increased after infusion of both drugs. The magnitude of the increase in ejection fraction was far greater with fenoldopam than with nitroprusside (+22% vs +8%; p = 0.04), despite a lesser reduction in systolic BP (−12 vs −22%, p = 0.002). Furthermore, the reduction in relative end-systolic volume (−35 vs −20%; p = 0.04), and increase in the ratio of peak systolic pressure to relative end-systolic volume (+43 vs +6%; p = 0.007) were greater after fenoldopam than after nitroprusside. The greater increment in parameters of LV systolic function produced by fenoldopam than by nitroprusside suggests an effect on LV performance that is independent of afterload reduction.

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Patients with severe systemic hypertension frequently need prompt therapy with parenteral agents to prevent target organ damage and even death.[1] The pharmacodynamic properties of nitroprusside make it an ideal agent for use in such emergencies, and it has become the standard against which new intravenous antihypertensive drugs are compared.[2] Nitroprusside therapy has the potential of thiocyanate toxicity,[3] may cause deterioration in renal function,[4] and can produce coronary steal owing to its nonspecific dilatation of conductance and capacitance vasculature.[5]

Fenoldopam mesylate reduces blood pressure (BP) and improves renal function by selective stimulation of vasodilatory dopamine-1 receptors of the systemic and renal vascular beds.[6–15] Previous comparative studies of fenoldopam and nitroprusside focused on BP and renal effects.[16–18] The relative impact of these agents on cardiac function has been less thoroughly investigated. This study was undertaken to compare the effects of fenoldopam with those of nitroprusside on radionuclide indexes of left ventricular (LV) systolic and diastolic functions in subjects with severe systemic hypertension.

METHODS

Fifty-six patients with severe untreated or uncontrolled hypertension were referred to the cardiology research clinic at the University of Tennessee from the emergency department of the Regional Medical Center at Memphis or from outpatient facilities operated by the Shelby County Health Department, charitable organizations and private practitioners. Screening studies for entry included a comprehensive history and physical examination, complete blood count, blood chemistries, urinalysis, chest roentgenogram and 12-lead electrocardiogram with rhythm strip. Patients were eligible to participate in the study if they were between the ages of 21 and 75 years, had diastolic BP ≥120 mm Hg, and no exclusion criteria were present (Table I). Of the 56 original referrals, 25 were excluded for medical reasons, and 12 declined to participate. The remaining 19 subjects constituted the study group. The study protocol was approved by the University's institutional review board, and each patient gave written informed consent.

The 19 subjects who met entry criteria were randomized to receive either fenoldopam or nitroprusside in an unblinded fashion. Initial infusion rates were 0.1 μg/kg/min of fenoldopam, and 0.5 μg/kg/min of nitroprusside. Titration proceeded in increments of 0.1 and

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1.0 μg/kg/min, respectively, until targeted BP was achieved (diastolic BP <110 mm Hg, or a ≥40 mm Hg reduction, if initial diastolic BP was ≥150 mm Hg).

Ten of the 19 randomized patients agreed to be studied a second time using the alternate drug at an average of 7.2 months (range 7 weeks to 24 months) after the initial study. Under close supervision, these patients were withdrawn from the oral antihypertensive regimen and were followed until diastolic BP met inclusion criteria. Therefore, a total of 29 patient studies were performed (15 with fenoldopam and 14 with nitroprusside).

BP was measured with an automated device (Dinemapp™, Critikon) using a cuff matched to upper arm circumference. Heart rate and cardiac rhythm were continuously monitored using a portable cardiac monitor-defibrillator (LifePak6™, PhysioControl). Baseline BP and heart rate values were determined as the averages of 3 measurements obtained at 5-minute intervals. During drug infusion, measurements were obtained 5 and 15 minutes after a change in infusion rate. After attainment of goal BP, final BP was determined as the average of 3 measurements obtained at 5-minute intervals.

A set of 2 gated radionuclide ventriculograms was obtained for each subject, the first during baseline BP determination, and the second after goal BP had been achieved. Gated radionuclide ventriculograms were obtained using a small field of view camera (LEM-ZLC, Siemens), a medium energy collimator, and commercial acquisition and analysis software (MicroDELTA+™ v7.1, Siemens) using standard techniques. Briefly, the blood pool was labeled in vivo with 25 mCi of technetium-99m pertechnetate 20 minutes after the injection of 15 mg of stannous pyrophosphate. A mid- (30 to 50°) left anterior oblique projection was selected, which provided the best separation of the right ventricular and LV blood pools. Caudal tilt of 5 to 10° was used to separate the left atrium from the left ventricle. Acquisition was continued until a total of 5 million counts was obtained for the entire field of view.

Data analysis: Background and LV regions of interest were drawn for each gated radionuclide ventriculogram using an automated edge detection algorithm. All regions were visually checked for accuracy and redrawn as necessary by an experienced observer. After background subtraction and smoothing, a time-activity curve and its first derivative curve were generated. LV ejection fraction was calculated as: (end-diastolic − end-systolic counts)/end-diastolic counts. Peak emptying and filling rates were determined as the rates of change at the most negative and positive extents, respectively, of the first derivative curve. The end-systolic pressure/count ratio was calculated by dividing the mean systolic BP during acquisition of the gated radionuclide ventriculogram by the number of counts contained in the LV region of interest at end-systole.

Within group changes were analyzed using 2-tailed paired *t* tests. Between group differences were analyzed using 2-tailed analysis of variance for continuous data, and chi-square tests for dichotomous data. Values are expressed as mean ± SD, unless otherwise indicated.

TABLE I Inclusion and Exclusion Criteria

Inclusion
Aged 21 to 75 years
Diastolic blood pressure > 120 mm Hg
Exclusion
Diastolic blood pressure > 170 mm Hg
Women of child-bearing potential
Known pheochromocytoma
Chronic liver disease
Elevation of liver enzymes or bilirubin > 50% above upper limits of normal
Clinical hypothyroidism
End-stage renal disease needing dialysis
Immunosuppressive therapy within past year
Use of phenothiazines or dopamine antagonists within 12 hours
Use of analgesics within 6 hours
Hypersensitivity to fenoldopam or nitroprusside

RESULTS

Group characteristics (Table II): There were no significant differences in baseline characteristics between those in the fenoldopam and nitroprusside groups. LV hypertrophy (defined as >5 points on the point score

TABLE II Group Characteristics at Baseline

	Overall	Nitroprusside	Fenoldopam	p Value*
No. of pts.	19	14	15	
Age (yr)	51 ± 11	50 ± 12	53 ± 11	0.53
Race—black (%)	18 (95)	14 (100)	14 (93)	0.33
Sex—women (%)	10 (53)	8 (57)	9 (60)	0.88
Left ventricular hypertrophy on electrocardiogram (%)	15 (79)	10 (71)	12 (80)	
Cardiomegaly on chest roentgenogram (%)	8 (19)	8 (57)	7 (47)	
Systolic blood pressure (mm Hg)	213 ± 16	216 ± 19	210 ± 13	0.33
Diastolic blood pressure (mm Hg)	131 ± 8	132 ± 8	129 ± 8	0.27
Heart rate (beats/min)	75 ± 14	76 ± 16	74 ± 12	0.72
Ejection fraction	0.53 ± 13	0.55 ± 0.12	0.52 ± 0.14	0.54
Peak filling rate (diastolic vol/s)	2.4 ± 0.8	2.5 ± 0.8	2.2 ± 0.9	0.34
End-systolic pressure/count ratio	0.030 ± 0.019	0.034 ± 0.023	0.027 ± 0.013	0.30

*Nitroprusside vs fenoldopam group.

TABLE III Changes in Blood Pressure and Heart Rate

Drug	Systolic Blood Pressure (mm Hg)		Diastolic Blood Pressure (mm Hg)		Heart Rate (beats/min)	
	Baseline	After Infusion	Baseline	After Infusion	Baseline	After Infusion
Fenoldopam	210 ± 13	184 ± 19*	129 ± 8	102 ± 7*	74 ± 12	90 ± 16*
Nitroprusside	216 ± 19	169 ± 13*	133 ± 8	97 ± 9*	74 ± 16	91 ± 22†

*p = 0.0001; †p = 0.002.

system of Romhilt and Estes)[19] was present in 15 subjects. Radiographic cardiac enlargement (as indicated by a cardiothoracic ratio >0.50 on the chest roentgenogram) was present in 8 patients.

Effects on heart rate and blood pressure (Table III and Figure 1): Both nitroprusside and fenoldopam lowered systolic and diastolic BP significantly. The mean durations of infusion needed to achieve goal BP were similar (58 ± 55 minutes for nitroprusside, and 65 ± 67 minutes for fenoldopam; p = 0.75). The magnitude of both systolic and diastolic pressure reduction was greater with nitroprusside than with fenoldopam (−47 mm Hg [−22%] vs −26 mm Hg [−12%] [p = 0.003], and −36 mm Hg [−27%] vs −28 mm Hg [−21%] [p = 0.03], respectively).

Heart rate increased modestly with both agents. There was no significant difference in the mean increase in heart rate between the 2 agents (+14.8 vs +15.4 beats/min; p = 0.88).

Systolic left ventricular performance (Figure 2): The baseline ejection fraction was 0.55 ± 0.12 in the nitroprusside group, and 0.52 ± 0.14 in the fenoldopam group (p = 0.54). Five patients in the nitroprusside group, and 7 in the fenoldopam group had baseline ejection fractions <0.50. After drug infusion, the ejection fraction in the nitroprusside group increased to 0.58 ± 0.13 (p = 0.09), and in the fenoldopam group to 0.61 ± 0.06 (p = 0.0002). The ejection fraction increased to a greater extent with fenoldopam than with nitroprusside (0.10 vs 0.03; p = 0.03).

Diastolic left ventricular performance: Diastolic performance was assessed using the gated radionuclide ventriculogram-derived peak filling rate. Baseline peak filling rate was similar for both groups (2.5 ± 0.8 diastolic volumes/s for the nitroprusside group vs 2.2 ± 0.9 diastolic volumes/s for the fenoldopam group). With treatment, the peak filling rate increased in both groups (3.1 ± 1.0 diastolic volumes/s [p = 0.07] with nitroprusside, and 2.8 ± 0.9 diastolic volumes/s [p = 0.01] with fenoldopam). The magnitude of the increase was similar for both groups (p = 0.81).

We compared the changes in relative end-diastolic and end-systolic volumes using a count-based method.[20–22] End-diastolic counts were reduced by a similar amount with nitroprusside and fenoldopam, decreasing by 14 and 17%, respectively (p = 0.67). Nitroprusside decreased end-systolic counts by only 2% compared with 35% (p = 0.04) with fenoldopam. Furthermore, the ratio of peak systolic pressure to end-systolic counts increased by only 6% after nitroprusside compared with an increase of 43% after fenoldopam (p = 0.006). This disparity was even larger in the subgroup with LV dysfunction in whom nitroprusside decreased the ratio by 7%, while fenoldopam increased it by 54% (p = 0.02) (Figure 1).

DISCUSSION

Similar to previous reports, our study demonstrates that fenoldopam can effectively lower systolic and diastolic BP in patients with severe systemic hypertension.[10–15] Fenoldopam was well-tolerated and compared favorably with nitroprusside in potency and safety. We noted no significant adverse effects, and in no case was fenoldopam discontinued owing to lack of efficacy, tachyphylaxis or undue hypotension.

Prior hemodynamic studies of fenoldopam produced discordant results. Ventura et al[12] studied 14 patients with mild essential hypertension using M-mode echocardiography, and intraarterial and venous catheters to measure cardiac output. They noted an increase in car-

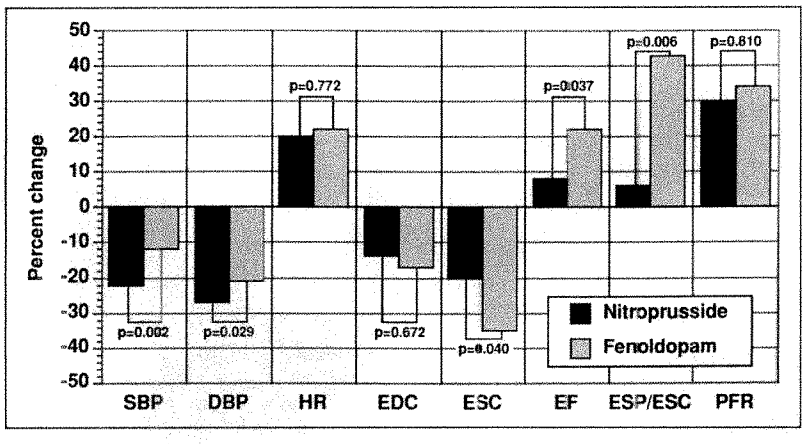


FIGURE 1. Bar graph showing comparison of percent changes in hemodynamic and nuclear angiographic parameters between fenoldopam and nitroprusside. Nitroprusside caused greater reduction in systolic and diastolic blood pressures than did fenoldopam. Fenoldopam increased ejection fraction and ratio of end-systolic blood pressure to volume to a greater extent than did nitroprusside. Relative end-systolic volume also decreased more with fenoldopam than with nitroprusside. DBP = diastolic blood pressure; EDC = end-diastolic counts; EF = ejection fraction; ESC = end-systolic counts; ESP/ESC = end-systolic pressure/count ratio; HR = heart rate; PFR = peak filling rate; SBP = systolic blood pressure.

diac output, heart rate, LV ejection rate, and circumferential fiber and fractional shortening accompanying a decrease in BP. In contrast, White et al[11] found no significant increase in fractional shortening by M-mode echocardiography in 9 patients with severe accelerated hypertension treated with fenoldopam.

As with fenoldopam, hemodynamic studies of nitroprusside have been inconsistent. Whereas cardiac output has been shown to increase with nitroprusside infusion in dogs,[23] clinical studies in humans have variably shown increases, reductions or no change in cardiac output.[24,25] Styles et al[25] found that nitroprusside restored cardiac output depressed by thiopental anesthesia. Furthermore, salutary effects of nitroprusside in various forms of LV dysfunction have been amply demonstrated.[26] Thus, the effect of nitroprusside on LV performance may depend on baseline LV function.

In our patients, both nitroprusside and fenoldopam improved parameters of systolic function. However, the magnitude of improvement in indexes of LV systolic function after fenoldopam was significantly greater than that after nitroprusside. Whereas infusion of nitroprusside increased baseline ejection fraction by a modest 0.03, fenoldopam produced an increase of 0.10 ($p = 0.03$).

Ejection phase indexes of ventricular function, such as ejection fraction, are dependent not only on the inotropic state of the ventricle, but on heart rate and loading conditions as well.[27] In our subjects, the magnitude of heart rate changes with each agent was similar. Systolic BP, a major component of afterload, actually decreased to a greater extent after nitroprusside than after fenoldopam (−22 vs −12%; $p = 0.002$). Although we did not directly measure end-diastolic pressure or volume, preload (as estimated by end-diastolic counts) decreased to a similar extent with each agent. If the improvement in ejection fraction after fenoldopam is due to natriuresis and diuresis, one would expect a greater reduction in preload compared with that with nitroprusside. Furthermore, Young et al[28] and Green et al[29] recently observed that decreases in systemic vascular resistance, and increases in cardiac index produced by fenoldopam in patients with congestive heart failure were not accompanied by significant changes in preload. We found that relative end-systolic volume (as denoted by end-systolic counts) decreased by 35% with fenoldopam, but only 2% with nitroprusside ($p = 0.04$). These changes in end-systolic volume are consistent with the observations of White et al[11] who noted a significant decrease in end-systolic dimension by echocardiography after fenoldopam. Although end-systolic volume is sensitive to afterload, it appears to be relatively insensitive to preload.[30] Thus, it appears that the greater improvement in ejection fraction observed after fenoldopam cannot be explained by changes in chronotropy, preload or afterload.

To further exclude group differences in preload and afterload, we constructed ratios of peak systolic pressure to end-systolic counts to obtain an index of systolic function relatively independent of loading.[31] This index increased by 43% after fenoldopam infusion compared with only 6% after nitroprusside ($p = 0.007$). As was the case with the increase in ejection fraction, the disparity between the 2 agents was even greater in patients with LV dysfunction (54 vs 7%; $p = 0.02$).

The mechanism underlying these observations is speculative. Hahn et al[7] found no evidence of a direct inotropic effect of fenoldopam on a papillary muscle preparation. Although Ventura et al[12] and Young et al[28] did not demonstrate any increase in plasma catecholamines, other investigators demonstrated a significant increase in norepinephrine after fenoldopam.[11,14] As stated by White et al,[11] whether fenoldopam has direct or indirect positive inotropic properties in patients with severe hypertension and hypertensive heart disease remains to be established.

Several limitations of our study warrant comment. For patient safety concerns, the study was unblinded. This may have allowed observational bias. However, the radionuclide ventriculograms were processed without knowledge of the agent used, which would have minimized important bias. The crossover design could have produced a crossover effect. The extended period between individual patient studies should have limited

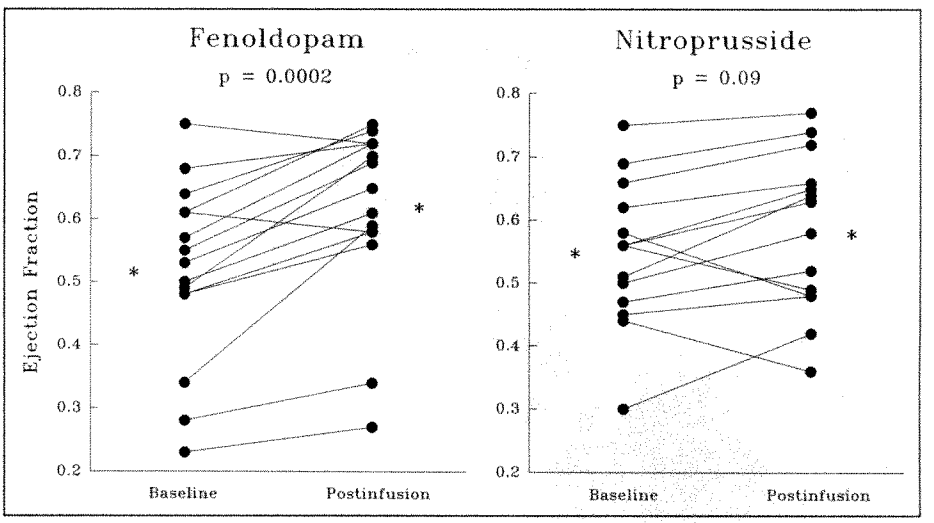


FIGURE 2. Individual changes in ejection fraction after fenoldopam *(left)* and nitroprusside *(right)*. Thirteen of 15 patients after fenoldopam, and 11 of 14 after nitroprusside had increased ejection fractions. *Asterisks* indicate changes in mean values.

such an effect. The number of counts on the nuclear angiogram cannot be used to represent absolute LV volume. However, changes in LV counts have been shown to accurately represent relative volume changes in the same patient over time.[20–22] We used the fractional change in the end-systolic pressure/count ratio as a derived index of contractility independent of loading conditions. This ratio only represents a point on a curve describing the end-systolic pressure/volume relation, and therefore, only incompletely describes such a relation.[30] However, Mehmel et al[32] did report reasonable correlation between the ratio and the slope (k) of the end-systolic pressure/volume relation. Furthermore, as we were primarily interested in the relative change in this relation, precise measurement of the slope was not needed. However, confirmation of our data using complete pressure/volume loops would be desirable. Finally, subjects participating in this study were highly selected volunteers with severe systemic hypertension and relatively good baseline ejection fractions (mean 0.53). Extrapolation of our data to other groups of patients with other forms of heart disease may not be appropriate.

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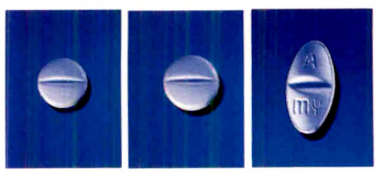
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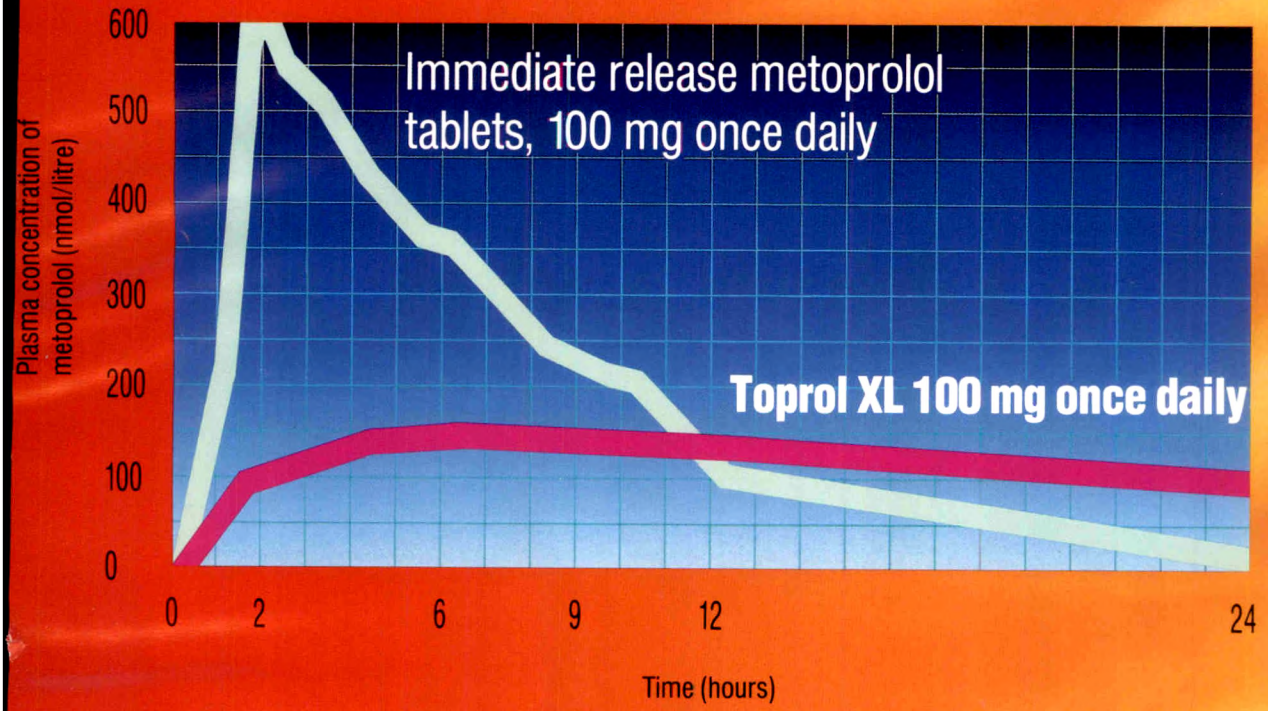
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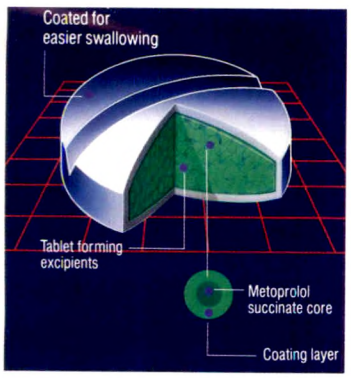
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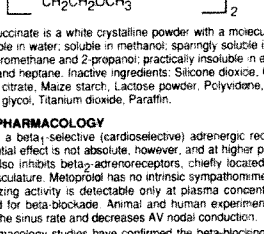
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Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane. Inactive ingredients: Silicone dioxide, Cellulose compounds, Acetyltributyl citrate, Maize starch, Lactose powder, Polyvidone, Magnesium stearate, Polyethylene glycol, Titanium dioxide, Paraffin.

CLINICAL PHARMACOLOGY

Metoprolol is a beta$_1$-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The relative beta$_1$-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the beta$_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent beta$_1$-receptor blocking doses.

In five controlled studies in normal healthy subjects, the same daily doses of Toprol XL and immediate release metoprolol were compared in terms of the extent and duration of beta$_1$-blockade produced. Both formulations were given in a dose range equivalent to 100–400 mg of immediate release metoprolol per day. In these studies, Toprol XL was administered once a day and immediate release metoprolol was administered once to four times a day. A sixth-controlled study compared the beta$_1$-blocking effects of a 50 mg daily dose of the two formulations. In each study, beta$_1$-blockade was expressed as the percent change from baseline, in exercise heart rate following standardized submaximal exercise tolerance tests at steady state. Toprol XL administered once a day, and immediate release metoprolol administered once to four times a day, provided comparable total beta$_1$-blockade over 24 hours (area under the beta$_1$-blockade versus time curve) in the dose range 100-400 mg. At a dosage of 50 mg once daily, Toprol XL produced significantly higher total beta$_1$-blockade over 24 hours than immediate release metoprolol. For Toprol XL, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of beta$_1$-blockade increased with increasing doses from 50 to 300 mg daily. The effects at peak/trough (i.e. at 24 hours post dosing) were; 14/9, 16/10, 24/14, 27/22 and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg Toprol XL once a day, respectively. In contrast to Toprol XL immediate release metoprolol given at a dose of 50–100 mg once a day, produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with Toprol XL over the dosing range of 200 to 400 mg, a t.i.d. to q.i.d. divided dosing regimen was required for immediate release metoprolol.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using the E_{max} model, the maximal beta$_1$-blocking effect has been estimated to produce a 28.3% reduction in exercise heart rate. Beta$_1$-blocking effects in the range of 30–80% of the maximal effect (corresponding to approximately 8–23% reduction in exercise heart rate) are expected to occur at metoprolol plasma concentrations ranging from 30–540 nmol/L. The concentration-effect curve begins reaching a plateau between 200–300 nmol/L, and higher plasma levels produce little additional beta$_1$-blocking effect. The relative beta$_1$-selectivity of metoprolol diminishes and blockade of beta$_2$-adrenoceptors increases at higher plasma concentrations.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta$_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

In controlled clinical studies, an immediate release dosage form of metoprolol has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics at dosages of 100–450 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable β_1-blockade as conventional metoprolol tablets administered two to four times daily. In addition, Toprol XL administered at a dose of 50 mg once daily has been shown to lower blood pressure 24-hours post-dosing in placebo controlled studies. In controlled, comparative, clinical studies, immediate release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyldopa, and thiazide-type diuretics, and to be effective both in supine and standing positions. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

Angina Pectoris

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardia contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

In controlled clinical trials, an immediate release formulation of metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable β_1-blockade as conventional metoprolol tablets administered two to four times daily.

Pharmacokinetics

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Toprol XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once daily administration of Toprol XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Toprol XL, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24 hour dosing interval, β_1-blockade is comparable and dose-related (see CLINICAL PHARMACOLOGY). The bioavailability of metoprolol shows a dose-related, although not directly proportional increase with dose and is not significantly affected by food following Toprol XL administration.

INDICATIONS AND USAGE

Hypertension

Toprol XL tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Toprol XL tablets are indicated in the long-term treatment of angina pectoris.

CONTRAINDICATIONS

Hypertension and Angina

Toprol XL is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Toprol XL should be administered cautiously. Both digitalis and Toprol XL slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Toprol XL should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta$_1$-selectivity, however, Toprol XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$-selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol XL should be used (see DOSAGE AND ADMINISTRATION).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Toprol XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Toprol XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PRECAUTIONS

General

Toprol XL should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Toprol XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Toprol XL without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol XL.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol XL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Risk Of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient. The following adverse reactions have been reported for metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol XL.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

No overdosage has been reported with Toprol XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since Toprol XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to Toprol XL.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly. On the basis of the pharmacologic actions of metoprolol tartrate, the following general measures should be employed.

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Toprol XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to Toprol XL, the same total daily dose of Toprol XL should be used.

As with immediate release metoprolol, dosages of Toprol XL should be individualized and titration may be needed in some patients.

Hypertension

The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Angina Pectoris

The dosage of Toprol XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).

HOW SUPPLIED

Tablets 50 mg:
Contain 47.5 mg of metoprolol succinate equivalent to 50 mg of metoprolol tartrate, USP
Are white, biconvex, round, film-coated
Engraved $\frac{A}{Mo}$ on one side and scored on the other

Bottles of 100 NDC 0186-1090-05

Tablets 100 mg:
Contain 95 mg of metoprolol succinate equivalent to 100 mg of metoprolol tartrate, USP
Are white, biconvex, round, film-coated
Engraved $\frac{A}{ms}$ on one side and scored on the other

Bottles of 100 NDC 0186-1092-05

Tablets 200 mg:
Contain 190 mg of metoprolol succinate equivalent to 200 mg of metoprolol tartrate, USP
Are white, biconvex, oval, film-coated
Engraved $\frac{A}{ny}$ and scored on one side

Bottles of 100 NDC 0186-1094-05

Store at controlled room temperature 15°–30°C (59°–86°F)

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:

ASTRA® | Astra Pharmaceutical Products, Inc
Westborough, MA 01581-4500

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FOOTNOTES:

1. Please see full prescribing information above.
2. Sandberg A, Blomqvist I, Jonsson UE, Lundborg P, Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol; a comparison with conventional tablets. Eur J Clin Pharmacol 1988; 33 (Suppl); S9-S14.
3. Data on file at AB Hassle.

Comparison of Angiotensin-Converting Enzyme Inhibitors and Calcium Antagonists in the Treatment of Mild to Moderate Systemic Hypertension, According to Baseline Ambulatory Blood Pressure Level

Daniel Herpin, MD, Bernard Vaisse, MD, Muriel Pitiot, Régis de Gaudemaris, MD, Jean-Michel Mallion, MD, Louis Poggi, MD, and Jean Demange, MD

This study was aimed at determining whether baseline ambulatory blood pressure (BP) levels influence the efficacy of angiotensin-converting enzyme inhibitors and calcium antagonists in the same manner. Accordingly, the ambulatory BP recordings of 236 mild to moderate hypertensive patients who had previously entered a clinical trial and had received either a calcium antagonist (n = 121) or an angiotensin-converting enzyme inhibitor (n = 115) were reviewed. The inclusion criterion was a clinic diastolic BP between 95 and 115 mm Hg at the end of the placebo period. Patients were classified according to the difference between their observed and predicted ambulatory BP (the latter assessed by regressing the observed ambulatory BP on the clinic BP). Reduction in ambulatory systolic and diastolic BP seemed to be greater ($p < 0.0001$, $p = 0.01$) in patients receiving an angiotensin-converting enzyme inhibitor than in those who were given a calcium antagonist. However, analysis of variance showed (1) there was a significant interaction ($F = 6.37$ $p = 0.01$) between the pharmacologic class and the baseline systolic ambulatory BP; and (2) the difference in diastolic ambulatory BP reduction between both classes was no longer significant when adjusted for baseline diastolic ambulatory BP. In patients with higher than predicted ambulatory BP levels, angiotensin-converting enzyme inhibitors and calcium antagonists had roughly a similar effect (reduction in systolic BP, 9 ± 8% vs 7 ± 6%, p = not significant; reduction in diastolic BP, 11 ± 8% vs 8 ± 6%, p = not significant). By contrast, in patients with lower than predicted ambulatory BP, angiotensin-converting enzyme inhibitors decreased ambulatory BP more than calcium antagonists did (systolic BP, 8 ± 7% vs 1 ± 7%, $p < 0.0001$; diastolic BP, 5 ± 8% vs 2 ± 7%, $p = 0.04$). Finally, further analysis found the threshold of efficacy to be 120/80 mm Hg in patients receiving an angiotensin-converting enzyme inhibitor and 135/85 mm Hg in those receiving a calcium antagonist.

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There are marked discrepancies between ambulatory blood pressure (BP) measurements and office BP readings in evaluating antihypertensive drugs.[1–6] This may be partly related to some patients who are found to have hypertension by clinic methods but appear to be normotensive when studied by whole-day ambulatory monitoring. Weber et al[7] showed that diltiazem therapy decreased clinic BP in these patients but did not significantly affect their 24-hour average BP. Likewise, Lacourcière et al[8] found that isradipine had a minimal effect on ambulatory BP in patients with apparent hypertension. Both of these studies involved calcium antagonists. More recently Ashida and coworkers[9] drew attention to a possible "class effect" within a group of 41 patients. Nifedipine, a calcium antagonist, did not change ambulatory BP in the group with low ambulatory BP, whereas enalapril, an angiotensin-con-verting enzyme inhibitor decreased it, both in the group with low and the group with high ambulatory BP. This raises an essential question of practical importance: Does the efficacy of calcium antagonists depend on the baseline ambulatory BP level to a greater extent than the efficacy of angiotensin-converting enzyme inhibitors? In other words, could calcium antagonists and angiotensin-converting enzyme inhibitors be considered as antihypertensive and hypotensive medications, respectively? We thought a preliminary answer could be given by a large-scale retrospective study: some investigators were invited to combine their own data with those of ours.

METHODS

Patients: This study involved 236 outpatients (157 men and 79 women, average age 52 ± 10 years, [range 22 to 76]) with mild to moderate hypertension. These patients had been selected by 2 centers from 13 recent clinical trials meeting the following criteria: run-in placebo period of 2 to 4 weeks, active treatment (angiotensin-converting enzyme inhibitors or calcium antagonists) for 4 to 12 weeks, and clinical and ambulatory BP measurements obtained as indicated later. The patients

TABLE I Characteristics of the Clinical Trials Analyzed

Drug	Therapeutic Regimen	Duration of Active Treatment Phase (weeks)	No. of Pts.	No. of Trials
Angiotensin-Converting Enzyme Inhibitors				
Perindopril	4–8 mg once a day	12	21	2
Captopril	25–50 mg twice a day	12	10	2
Lisinopril	20 mg once a day	4–8	32	2
Enalapril	20 mg once a day	4	14	1
Fosinopril	20 mg once a day	6	38	1
Calcium Antagonists				
Diltiazem SR	240–300 mg once a day	4–6	50	2
Nicardipine SR	50 mg twice a day	4	10	1
Nitrendipine	20 mg once a day	4	51	1
Verapamil SR	240 mg once a day	4	10	1

TABLE II Patient Characteristics in Angiotensin-Converting Enzyme Inhibitor and Calcium Antagonist Groups

	ACE Inhibitors	CA
No. of patients	115	121
Men/women	81/34	76/45
Mean age (yr)	51 ± 10	52 ± 10
Baseline clinic BP (mm Hg)	164/104 ±14/±6	163/102 ±17/±6
Baseline ambulatory BP (mm Hg)	139/90 ±13/±8	141/89 ±16/±10

Differences were not significant.
ACE = angiotensin-converting enzyme; BP = blood pressure; CA = calcium antagonists.

became eligible for the active phase of treatment if they had a clinic diastolic BP >95 and <115 mm Hg at the end of the placebo period. They gave informed consent before entering the trial. All patients had been diagnosed as having essential hypertension by exclusion of secondary forms by routine clinical means. No medications other than the test drug were given throughout the trials. One hundred fifteen patients were given an angiotensin-converting enzyme inhibitor, 121 patients received a calcium antagonist (Table I). The data were collected by 2 main centers.

Blood pressure measurements: Clinic BP was recorded in the supine position with a standard mercury sphygmomanometer and the average of 3 readings was taken for analysis; the first and fifth Korotkoff sounds were used as indications for systolic and diastolic BP, respectively. The visits were scheduled before the patients took their morning dose.

Automated ambulatory BP recordings were performed with portable monitors (Spacelabs 5 200, 90 202 or 90 207, Spacelabs Inc. Redmond, Washington). The cuff inflated at regular preset intervals (every 15 minutes from 6:00 A.M. to midnight, every 30 minutes from midnight to 6:00 A.M.). Individual readings showing a diastolic BP >150 mm Hg and those with a pulse pressure <10 mm Hg were not considered for analysis. All readings within each 1-hour period were averaged and 24-hour BP was expressed for each patient as the mean of these 24 values. All recordings with >2 missing 1-hour periods were discarded. Patients were classified into 2 groups according to the method of Perloff et al,[10] as modified by Ashida et[9]: The "high ambulatory BP group" was defined by an average 24-hour BP higher than the level predicted from the regression line between observed 24-hour and clinic BPs; the other patients were designated as the "low ambulatory BP group."

Statistics: All data were computerized and statistical analyses were performed using statistical BMDP software (programs 1D, 3D, 6D, 4F, 2V, 1R). Comparisons of patients' characteristics and BP measurements between groups (angiotensin-converting enzyme inhibitors versus calcium antagonists or low versus high BP groups) were performed using Student's t test or nonparametric Wilcoxon's test when necessary; Pearson's chi-square was used for categorical data. Comparisons between drug-induced changes in 24-hour ambulatory BP were performed by means of an analysis of variance. In addition to the pharmacologic class (angiotensin-converting enzyme inhibitor or calcium antagonist), baseline ambulatory BP level (lower or higher than "expected"), age (<40, 40 to 49, 50 to 59 and >60 years) and center were taken into account as qualitative independent variables. Furthermore, an interaction was sought between the pharmacologic class and each of the other independent variables, its significance being expressed by an F ratio. Finally, clinic BP and changes in ambulatory BP were correlated with baseline ambulatory BP by means of Pearson's correlation test. Changes in BP are given as percentages of baseline levels. Results are expressed as mean ± standard deviation. The 5% level of statistical significance was adopted for all tests.

RESULTS

Patients characteristics are listed in Table II. Both groups did not differ in gender, age or baseline clinic and ambulatory BP, even after adjustment for center.

Changes in systolic blood pressure: Mean reduction in clinic systolic BP was 11 ± 10% and 9 ± 9% (p = not significant [NS]), whereas ambulatory systolic BP decreased by 9 ± 7% and 5 ± 7% (p <0.0001) in the groups taking angiotensin-converting enzyme inhibitors and calcium antagonists, respectively. However, analysis of variance showed a significant interaction between pharmacologic class and the baseline ambulatory systolic BP level ($F = 6.37$ $p = 0.01$ after adjustment for class, baseline level, center and age; $F = 5.12$ $p = 0.02$ without adjusting for center. The effects of both pharmacologic classes have then to be analyzed within each subset according to baseline systolic BP level (Table III); the difference between both classes was still significant only in the group with low BP. As a corollary, the correlation between baseline ambulatory BP level and percentage of reduction in ambulatory systolic BP appeared to be much closer in the group taking calcium antagonists ($r = 0.48$ $p < 0.0001$) than in those taking

TABLE III Age and Systolic Blood Pressure Measurements According to Drug and Baseline Ambulatory Level

	Low Ambulatory Systolic BP Group		High Ambulatory Systolic BP Group	
	ACE Inhibitors (subgroup 1)	CA (subgroup 2)	ACE Inhibitors (subgroup 3)	CA (subgroup 4)
No. of patients	62	51	53	70
Mean age (yr)	51 ± 9	54 ± 9	51 ± 10	51 ± 10
Baseline clinic systolic BP (mm Hg)	163 ± 12	163 ± 17	166 ± 17	162 ± 16
Baseline ambulatory systolic BP (mm Hg)	130 ± 7	127 ± 12	150 ± 10*	150 ± 12†
Reduction in clinic systolic BP (%)	13 ± 9‡	13 ± 8‡	9 ± 10§	7 ± 9‖
Reduction in ambulatory systolic BP (%)	8 ± 7	1 ± 7*	9 ± 8	7 ± 6†

*$p < 0.0001$ versus subgroup 1; †$p < 0.0001$ versus subgroup 2; ‡$p < 0.0001$ versus reduction in ambulatory systolic blood pressure; §$p = 0.04$ versus subgroup 1; ‖$p = 0.0003$ versus subgroup 2.
Abbreviations as in Table II.

TABLE IV Age and Diastolic Blood Pressure Measurements According to Drug and Baseline Ambulatory Level

	Low Ambulatory Diastolic BP Group		High Ambulatory Diastolic BP Group	
	ACE Inhibitors (subgroup 1)	CA (subgroup 2)	ACE Inhibitors (subgroup 3)	CA (subgroup 4)
No. of patients	57	61	58	60
Mean age (yr)	51 ± 10	55 ± 9*	52 ± 9	50 ± 9†
Baseline clinic diastolic BP (mm Hg)	104 ± 7	101 ± 6‡	103 ± 6	103 ± 6
Baseline ambulatory diastolic BP (mm Hg)	85 ± 6	81 ± 6§	96 ± 7‖	97 ± 7¶
Reduction in clinic diastolic BP (%)	13 ± 8**	13 ± 8**	10 ± 8††	9 ± 7‡‡
Reduction in ambulatory diastolic BP (%)	5 ± 8	2 ± 7††	11 ± 8§§	8 ± 6¶

*$p = 0.03$ versus subgroup 1; †$p = 0.006$ versus subgroup 2; ‡$p = 0.01$ versus subgroup 1; §$p = 0.002$ versus subgroup 1; ‖$p < 0.0001$ versus subgroup 1; ¶$p < 0.0001$ versus subgroup 2; **$p < 0.0001$ versus reduction in ambulatory diastolic blood pressure; ††$p = 0.04$ versus subgroup 1; ‡‡$p = 0.003$ versus subgroup 2; §§$p = 0.0007$ versus subgroup 1.
Abbreviations as in Table II.

angiotensin-converting enzyme inhibitors ($r = 0.19$ $p = 0.04$). Furthermore, changes in clinic systolic BP were significantly more marked in the group with low rather than high systolic BP; thus, clinic systolic BP decreased significantly more than ambulatory systolic BP only in the group with low systolic BP.

Changes in diastolic blood pressure: Clinic diastolic BP decreased by 11 ± 8% and 11 ± 8% (p = NS) and ambulatory diastolic BP by 8 ± 8% and 5 ± 7% ($p = 0.01$) in patients treated with an angiotensin-converting enzyme inhibitor and those receiving a calcium antagonist, respectively. This "class effect" was still significant after adjustment for center and age but became no longer significant when adjusted for baseline ambulatory diastolic BP level ($F = 2.61$, p = NS). There was a lack of difference between the effects of both classes within the group with high diastolic BP, but angiotensin-converting enzyme inhibitors were significantly more effective than calcium antagonists within the group with low diastolic BP (Table IV). The correlation coefficients between baseline ambulatory diastolic BP and changes in diastolic BP were 0.37 and 0.46 in the groups taking angiotensin-converting enzyme inhibitors and calcium antagonists, respectively. As observed with systolic BP, the reduction in clinic diastolic BP was more pronounced in the group with low rather than high diastolic BP; consequently, clinic diastolic BP decreased significantly more than ambulatory diastolic BP only in the group with low diastolic BP.

Threshold of efficacy: Finally, baseline ambulatory systolic and diastolic BP levels have been divided into 9 and 6 consecutive 5 mm Hg intervals, respectively. A statistical analysis of the mean effect of both pharmacologic classes was performed within each interval and a threshold of efficacy could then be determined. Mean changes in ambulatory BP appeared not to be significant up to 120 and 80 mm Hg in the group taking angiotensin-converting enzyme inhibitors, and up to 135 and 85 mm Hg in those taking calcium antagonists, for systolic BP and diastolic BP, respectively.

DISCUSSION

Method: This retrospective study has some methodologic limitations. None of the trials was aimed at comparing an angiotensin-converting enzyme inhibitor versus a calcium antagonist according to the baseline ambulatory BP level, so that the drug allocation was not randomized at all. Furthermore, we combined several drugs with different pharmacokinetics into 2 joint groups and we cannot assure there was a strict bioequivalence between them. However, the doses that were given were those generally recommended in clinical practice. We can observe that angiotensin-converting enzyme inhibitors and calcium antagonists resulted in a reduction in clinic BP of the same extent (Tables III and IV), which supports existing published studies.[6,9,11] On the other hand, the large number of patients recruited made it possible to constitute relatively homogenous

groups, regarding demographic characteristics and baseline BP.

Changes in blood pressure according to drug and baseline blood pressure: The striking feature of this analysis was that angiotensin-converting enzyme inhibitors apparently decreased ambulatory BP to a greater degree than calcium antagonists. Importantly, adjustment for baseline ambulatory BP level led one to (1) emphasize a significant interaction between the pharmacologic class and the baseline systolic BP level; and (2) no longer observe a significant difference in diastolic BP changes between both classes. Both features had the same meaning: angiotensin-converting enzyme inhibitors actually were more effective than calcium antagonists only in patients with low baseline ambulatory BP. In this respect, our results were fully consistent with those reported by Ashida et al.[9] However, an original feature of our study has to be pinpointed. The difference between the effects of angiotensin-converting enzyme inhibitors and calcium antagonists was not as clear-cut in the group with low diastolic BP as in those with low systolic BP. BP changes, as induced by angiotensin-converting enzyme inhibitors, were indeed of the same degree in both groups with high and low systolic BP, but were more marked in the group with high than in those with low diastolic BP ($p = 0.0007$). The correlation found between baseline BP and the effects of angiotensin-converting enzyme inhibitors was consistently much closer for diastolic than for systolic BP.

The underlying mechanisms of such a phenomenon are still open to discussion[12,13]: One can speculate that arteriolar smooth muscle tone (which determines diastolic BP level) is under the control of both the renin-angiotensin system and free cytosolic calcium (the former perhaps playing a preeminent role in "white coat" hypertensive patients); furthermore, the compliance of the great vessels (which regulates systolic BP) could be determined almost exclusively by the local tissue renin-angiotensin system in such patients. Sodium balance should also be considered as playing a role in the differences we observed, because salt repletion results in opposite effects on the efficacy of angiotensin-converting enzyme inhibitors and calcium antagonists.[14] However, sodium intakes could not be strictly controlled in our outpatients. The opposition between calcium antagonists as antihypertensive drugs and angiotensin-converting enzyme inhibitors as hypotensive drugs could possibly be kept in mind regarding systolic BP; but does not seem to be relevant with regard to diastolic BP.

Clinical implications: First, practical information has to be drawn from these results: Antihypertensive drug effects seem to be overestimated by conventional BP measurements, but tend to be minimized by ambulatory recordings if the patient group is considered as a whole. Clinical investigators should assess true hypertensive patients separately from those with "normal" ambulatory BP in order to avoid the real effects of a drug to be "diluted."[7] Our results suggest that such a phenomenon especially concerns calcium antagonists but may also occur with angiotensin-converting enzyme inhibitors (see Table IV): Cheung et al[15] consistently showed that patients who did not respond to combined therapy with captopril and hydrochlorothiazide were those with the lowest ambulatory BP.

Second, what about the "white coat hypertensive" patients receiving an antihypertensive drug? The brain is well protected against reductions in mean arterial pressure, especially in normotensive subjects,[16] and the left coronary artery is exclusively perfused during diastole; therefore, a visceral hypoperfusion is unlikely to occur during treatment with calcium antagonists or even with angiotensin-converting enzyme inhibitors, since both drugs have been shown not to be significantly effective in patients with a baseline ambulatory diastolic BP <85 or <80 mm Hg, respectively. These pressure levels are above the critical perfusion pressure,[17] at least in patients without any arterial stenosis.

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‡ In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

ACCUPRIL is available in 10, 20, and 40 mg tablets. Usual initial starting dosage is 10 mg once daily.

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Please see brief summary of prescribing information on following page.

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Accupril® (Quinapril Hydrochloride Tablets)

Before prescribing, please see full prescribing information. A brief summary follows.

INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m², respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).



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Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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Effect of Aortic Valve Stenosis (Pressure Overload) and Regurgitation (Volume Overload) on Left Ventricular Systolic and Diastolic Function

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In secondary hypertrophy from chronic pressure or volume overload, or both, systolic as well as diastolic abnormalities of left ventricular (LV) function have been described, but their relation has not been defined. In 58 patients with aortic valve disease (28 with aortic valve stenosis, and 30 with aortic regurgitation) and in 11 control subjects, LV biplane cineangiography was performed simultaneously with LV high-fidelity pressure measurements. LV ejection performance was assessed by ejection fraction, and diastolic function by the time constant of LV pressure decay, the early and late peak filling rates, and the constants of chamber (pressure-volume relation) and myocardial stiffness (stress-strain relation).

In the entire cohort (n = 69), ejection fraction was inversely related to the time constant of LV relaxation ($r = -0.58$, $p < 0.001$) and to the constant of myocardial stiffness ($r = -0.62$, $p < 0.001$). Despite preserved systolic contractile function (as evaluated from the ejection fraction–mean systolic stress relation), abnormalities in LV diastolic function were present in 9 of 18 patients with pressure overload and 20 of 22 with volume overload. None of the 58 patients with aortic valve disease had a reduced early peak filling rate, whereas a reduction in late peak filling rate was observed in 3 with aortic stenosis, but in none with aortic regurgitation.

Thus, it appears that abnormalities of relaxation and passive diastolic myocardial stiffness precede alterations in myocardial contractility. Assessment of peak filling rates is not helpful to detect diastolic dysfunction in patients with aortic valve disease.

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Myocardial hypertrophy is an adaptive process that tends to normalize elevated wall stress and to preserve systolic pump function of the heart. It has to be recognized that compensatory mechanisms, such as hypertrophy, may influence adversely left ventricular (LV) diastolic function.[1] The effect of overload hypertrophy on systolic and diastolic function was studied extensively in the past,[1–7] but their interrelation has not been defined clearly. The interplay between inotropic and lusitropic effects, as well as between diastolic passive elastic properties and systolic ejection performance, is complex and has not been evaluated in the clinical setting. Furthermore, previous reports showed conflicting results concerning the adaptation of the left ventricle to pressure or volume overload.[2–7] Murakami et al[2] demonstrated that LV filling may vary depending on the degree of LV hypertrophy and systolic ejection performance in patients with aortic stenosis. Osbakken and Bove[3] reported that abnormal diastolic function was associated with a reduction in systolic ejection function in severe volume overload. More recently, Corin and et al[4] showed an inverse relation between the constant of myocardial stiffness and systolic ejection fraction in patients with mitral regurgitation. In the present study, the relation between measures of LV systolic and diastolic function was investigated in patients with aortic valve disease.

METHODS

Patients: Fifty-eight patients (24 women and 34 men, mean age 50 ± 13 years, range 18 to 72) with severe aortic valve disease, and 11 controls subjects (mean age 48 ± 12 years, range 38 to 65) were included in the present analysis. Patients were divided into 3 groups: group 1 consisted of 11 patients (5 women and 6 men) who were evaluated for atypical chest pain and were found to have no cardiovascular disease; group 2 consisted of 28 patients (11 women and 17 men) with aortic stenosis (mean aortic valve area 0.61 cm^2, range 0.36 to 1.0; regurgitant fraction <15%); and group 3 consisted of 30 patients (13 women and 17 men) with pure or predominant aortic regurgitation (mean regurgitant fraction 57%, range 35 to 72; aortic valve area >1.10 cm^2). Mean age was not different in the 3 groups. Mean New York Heart Association functional class was 1.7 ± 0.4 in the group with aortic stenosis, and 1.8 ± 0.5 in that with aortic regurgitation. Patients with coexistent mitral insufficiency or coronary artery

disease were excluded from the present study. All patients were in sinus rhythm.

Cardiac catheterization: Informed consent was obtained from all patients. Cardiovascular medications were withheld 12 to 24 hours before the procedure. Premedication consisted of chlordiazepoxide (10 mg) given orally 1 hour before catheterization. Right and left heart catheterization was performed in all cases. Biplane left ventriculography was performed in the right (30-degree) and left (60-degree) anterior oblique projection (Cardioscope, Siemens-Albis, Zurich, Switzerland) at a filming rate of 50 frames/s. LV pressure was measured simultaneously with ventriculography by means of a Millar 7Fr micromanometer-catheter introduced transseptally into the left ventricle with an 11.5Fr Brockenbrough guiding catheter. Central aortic pressure was measured through a fluid-filled 8Fr pigtail catheter. All pressures were recorded at a paper speed of 250 mm/s (Electronics for Medicine, VR-12) with a standard lead of the electrocardiogram, the first derivative of LV high-fidelity pressure (dP/dt) and the time marks corresponding with the digital numbers on the angiographic images.[2,4,6]

Left atrial pressure was measured transseptally before LV cineangiography. Left atrial v-wave pressure was considered to represent "mitral valve opening pressure." In control subjects (in whom left atrial pressure was not measured directly because no transseptal puncture was performed), mitral valve opening pressure was considered as the LV pressure occurring at the time at which unopacified blood first entered the ventricle in the angiogram. This pressure correlated well with the transseptally measured v-wave pressure.[2]

LV silhouettes were drawn manually from an adequately opacified sinus beat, excluding extrasystolic and postextrasystolic beats. LV volumes were determined on a frame-by-frame basis for 1 cardiac cycle using the area-length method.[8] Dimensional and volume data were filtered using the moving average technique.[2,4] LV pressure tracings were digitized for 1 cardiac cycle using an electronic digitizer (Numonics Corp., Montgomeryville, Pennsylvania) and interfaced to a computer (PDP-11/34, DEC, Maynard, Massachusetts). Pressure and volume data were analyzed every 20 ms for 1 cardiac cycle. End-diastole was defined as the time point of the rapid upstroke of dP/dt. End-systole was considered to occur at the time of aortic valve closure (incisural pressure). LV end-diastolic wall thickness and muscular mass were determined according to the method of Rackley et al.[9] Instantaneous LV wall thickness was calculated for each cineframe throughout the cardiac cycle using the method of Hugenholtz et al.[10]

Systolic function: Circumferential wall stress was calculated for each cineframe from a simplified version of Mirsky's thick wall model (see Appendix).[11] Mean systolic wall stress was defined as the wall stress occurring during the systolic ejection period.[12]

SUBGROUPS: Patients with aortic valve disease were grouped according to their actual level of systolic contractile function. Subgroup 2a consisted of 18 patients with aortic stenosis and normal contractility, and subgroup 2b of 10 patients with aortic stenosis and depressed contractile function. Subgroup 3a consisted of 22 patients with aortic regurgitation and normal contractile function, and subgroup 3b of 8 patients with aortic regurgitation and depressed contractility.

Normal systolic contractile function was defined on the basis of the ejection fraction–mean systolic wall stress relation.[12] The normal range and 95% prediction limits are given by the 11 control patients (Figure 1). Those patients with values below this range were considered to have depressed contractile function (Figure 1).

Diastolic function: Diastolic function was evaluated from isovolumic relaxation, peak diastolic filling rates and passive elastic properties.

LV relaxation was assessed from the time constant of isovolumic pressure decline beginning from maximum negative dP/dt and ending when pressure had decreased to 5 mm Hg above LV end-diastolic pressure.[13] Three different methods were used: (1) Time constant (τ_d) was calculated as the negative reciprocal of the slope of the linear relation between LV pressure and negative dP/dt, according to Raff and Glantz.[14] (2) Pressure-halftime (t_w = time until LV pressure at peak negative dP/dt decreased to 50% of its initial value) was determined from the exponential pressure-time relation with zero asymptote.[15] (3) Pressure–halftime (t_M) was

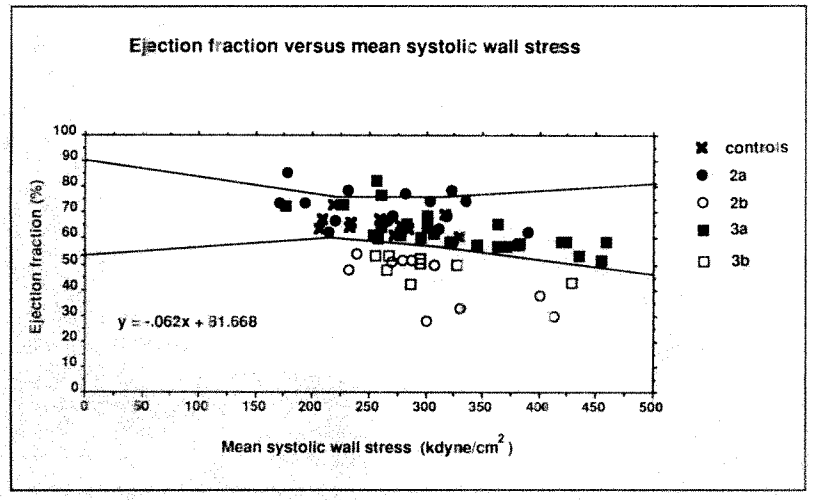


FIGURE 1. Afterload-shortening relationship for control subjects *(crosses)*, aortic stenosis with normal (group 2a, *closed circles*) and reduced (group 2b, *open circles*) systolic contractility, and aortic regurgitation with normal (group 3a, *closed squares*) and depressed (group 3b, *open squares*) contractility. Regression equation defined by control subjects, and 95% prediction limits of this regression are also shown.

TABLE I Systolic Function Parameters

	Control Subjects (n = 11)	Aortic Stenosis (n = 28)	Aortic Regurgitation (n = 30)
HR (beats/min)	75 ± 12	77 ± 13	74 ± 13
LVSP (mm Hg)	130 ± 14	212 ± 32‡§	147 ± 24
LVEDP (mm Hg)	11 ± 2	23 ± 9‡	20 ± 9†
EDVI (ml/m^2)	82 ± 15	95 ± 19§	195 ± 55‡
ESVI (ml/m^2)	28 ± 7	35 ± 17§	79 ± 31‡
EF (%)	66 ± 3	63 ± 15	60 ± 10
WTh (cm)	0.78 ± 0.07	1.30 ± 0.15‡§	1.07 ± 0.18‡
LMMI (g/m^2)	85 ± 14	169 ± 36‡	191 ± 46‡
SM (kdyne/cm^2)	257 ± 42	276 ± 57	306 ± 63*

*p <0.05, †p <0.01, ‡p <0.001 vs control subjects; §p <0.001 vs aortic regurgitation.
EDVI = end-diastolic volume; EF = ejection fraction; ESVI = end-systolic volume; HR = heart rate; LMMI = left ventricular mass; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular peak systolic pressure; SM = mean systolic circumferential wall stress; WTh = end-diastolic wall thickness.

TABLE II Diastolic Function Prameters

	Control Subjects (n = 11)	Aortic Stenosis (n = 28)	Aortic Regurgitation (n = 30)
Relaxation			
τ_d (ms)	43 ± 12	66 ± 25*	73 ± 23†
t_W (ms)	27 ± 6	34 ± 7	33 ± 6
t_M (ms)	29 ± 7	35 ± 8	34 ± 7
Filling			
MVOP (mm Hg)	10 ± 2	22 ± 12‡§	16 ± 9
PFR1 (ml/m^2/s)	269 ± 91	302 ± 96‖	462 ± 157‡
PFR2 (ml/m^2/s)	181 ± 44	248 ± 114‖	388 ± 201‡
Passive elastic properties			
b* (1/ml/m^2)	0.044 ± 0.026	0.070 ± 0.035§	0.040 ± 0.031
c* (mm Hg)	−0.5 ± 5.0	9.9 ± 8.2†	5.9 ± 7.7
b′	3.5 ± 1.8	10.5 ± 5.6*	7.7 ± 8.2
b	9.9 ± 3.3	20.4 ± 15.5*	26.9 ± 12.7†
c (kdyne/cm^2)	−0.7 ± 6.1	13.0 ± 11.4*	17.9 ± 18.2†

*p <0.05, †p <0.01, ‡p <0.001 vs control subjects; §p <0.05, ‖p <0.001 vs aortic regurgitation.
b = constant of myocardial stiffness; b* = constant of chamber stiffness; b′ = normalized constant of chamber stiffness; c = asymptote of the stress–strain relation; c* = asymptote of the pressure-volume relation; MVOP = mitral valve opening pressure; PFR1 and PFR2 = peak filling rates during the first and second half of diastole, respectively; τ_d = time constant calculated from the linear relation between pressure and negative dP/dt; t_M = pressure halftime calculated from exponential relation with shifting asymptote between pressure and time; t_W = pressure halftime calculated from exponential relation with zero asymptote between pressure and time.

calculated from the exponential pressure-time relation with shifting asymptote using the 3-constants model (see Appendix).[16]

Peak diastolic filling rate was defined as the largest value of diastolic inflow (ml/m^2/s); the greatest value occurring in the first half of diastole was termed the early peak filling rate and in the second half of diastole the late peak filling rate. The filling phase was considered to begin 20 ms before the first frame showing the entry of unopacified blood into the left ventricle and to end at end-diastole. Instantaneous diastolic filling rates were calculated every 20 ms after mitral valve opening (see Appendix). To minimize error due to random noise, raw data were filtered using the fifth-grade moving average.[2]

Passive elastic properties were determined during the period from minimum ventricular pressure to end-diastole. LV chamber (pressure-volume relation) and myocardial (stress-strain relation) properties were calculated in each patient, using an exponential model with shifting asymptote (see Appendix).[4-6]

The normal limits for each parameter are defined as mean value ± 2 SD obtained from the control group.

Statistics: Comparisons among control subjects, and patients with aortic stenosis and regurgitation were performed by 1-way analysis of variance. When the analysis was significant, the Scheffe procedure was applied. Linear regression analysis between measures of systolic and diastolic function was calculated by the least-squares method. Comparison of the various indexes of LV diastolic function in the 4 subgroups was performed by the chi-square procedure. In all tables, mean values ± 1 SD are given.

RESULTS

Systolic function data: Heart rate was not different among the 3 groups. Hemodynamic data of the 3 groups of patients are listed in Table I.

Diastolic function data: Diastolic function data of the 3 groups of patients are listed in Table II. A significant difference in τ_d between the 3 groups was observed. The pressure-halftimes t_W and t_M, were not different among the 3 groups.

Correlations between systolic and diastolic functions (Table III): In aortic stenosis, ejection fraction is

TABLE III Correlations Between Ejection Fraction and Indexes of Diastolic Function

	All Patients (n = 69)		Aortic Stenosis (n = 28)		Aortic Regurgitation (n = 30)	
	r	p Value	r	p Value	r	p Value
EF vs τ_d	−0.58	<0.001	−0.65	<0.001	−0.46	<0.01
EF vs t_W	−0.33	<.05	−0.32	NS	−0.31	NS
EF vs t_M	−0.28	<0.05	−0.23	NS	−0.32	NS
EF vs MVOP	−0.30	<0.05	−0.48	<0.01	0.04	NS
EF vs PFR1	0.18	NS	0.36	<0.05	0.48	<0.01
EF vs PFR2	0.36	<0.05	0.37	<0.05	−0.03	NS
EF vs b*	−0.04	NS	−0.11	NS	0.06	NS
EF vs c*	−0.29	<0.05	−0.33	NS	−0.27	NS
EF vs b′	−0.41	<0.01	−0.56	<0.01	−0.31	NS
EF vs b	−0.62	<0.001	−0.71	<0.001	−0.29	<0.05
EF vs c	−0.59	<0.001	−0.68	<0.001	−0.35	<0.05

NS = not significant; r = correlation coefficient; other abbreviations as in Tables I and II.

inversely related to τ_d, mitral valve opening pressure and the constant of myocardial stiffness, but is directly related to early and late peak filling rates. In aortic regurgitation, ejection fraction is inversely related to τ_d and to the constant of myocardial stiffness, but also directly related to peak filling rate during early diastole. In the entire cohort (n = 69) there was an inverse relation between ejection fraction and relaxation for all 3 methods used. However, the highest correlation was found using the derivative method (Figure 2).[14] There was also an inverse relation between ejection fraction and the constant of myocardial stiffness (Figure 3). Only a weak positive correlation was found between ejection fraction and late peak filling rate, whereas a poor negative correlation was evident between ejection fraction and mitral valve opening pressure (Figure 2). No correlation was found between ejection fraction and the constant of chamber stiffness (Figure 3), but there was a weak relation between ejection fraction and the constant of normalized chamber stiffness (Table III).

Diastolic function in patients with normal and depressed contractile function: Diastolic function data of the 4 subgroups of patients with normal and depressed contractile function are listed in Tables IV and V.

The incidence of abnormal diastolic function parameters in the 4 subgroups are shown in Figure 4. Of the 18 patients with aortic stenosis and normal systolic function (subgroup 2a), 6 (33%) had a prolonged (>67 ms = upper limit of normality) time constant of relaxation, none had a depressed early peak filling rate, 1 (6%) had a depressed late peak filling rate (<93 ml/m^2/s = lower limit of normality), and 5 (28%) had an increased (>16.5 = upper limit of normality) constant of myocardial stiffness. Of the 10 patients with aortic stenosis and depressed systolic function (subgroup 2b), (60%) had a prolonged time constant of LV pressure

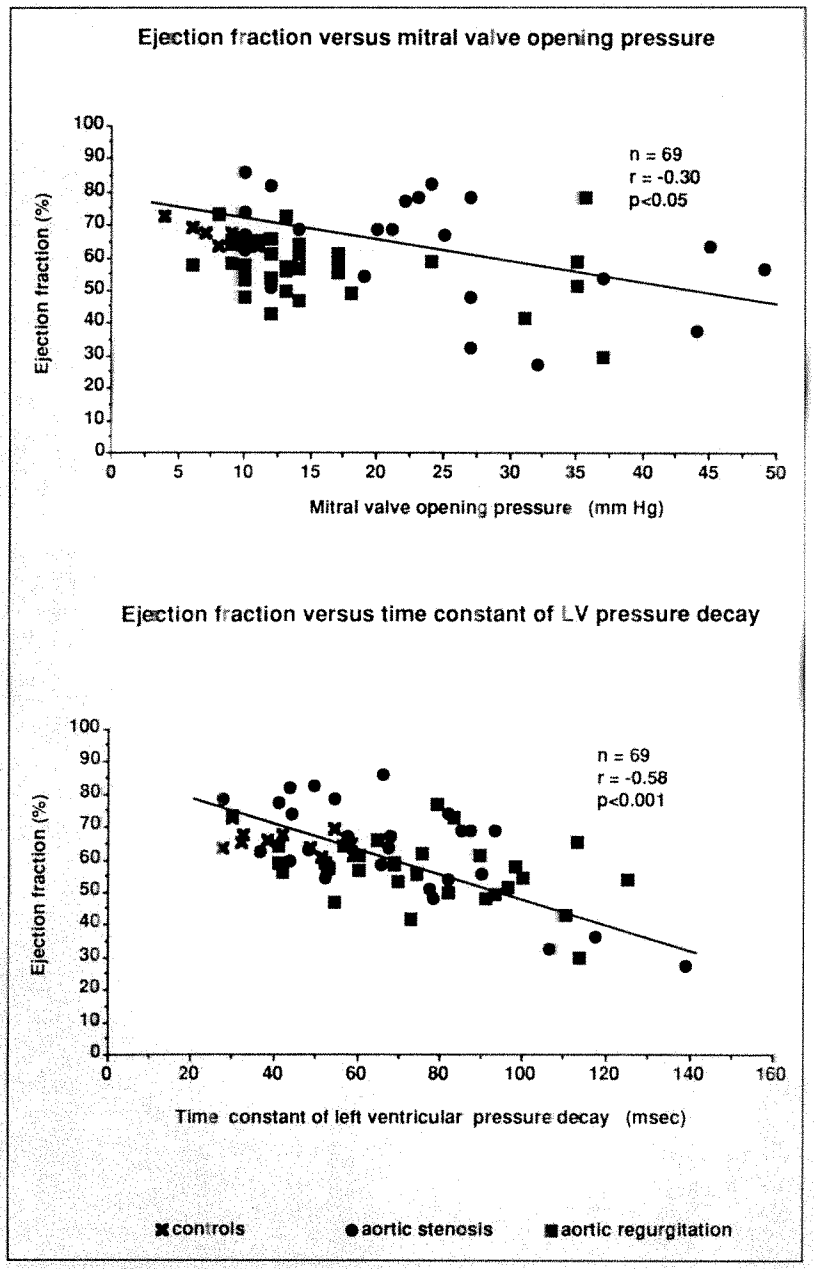


FIGURE 2. Inverse relations between ejection fraction and mitral valve opening pressure (*top*), and ejection fraction and time constant of left ventricular (LV) pressure decay (*bottom*).

decay, none had a depressed early peak filling rate, 2 (20%) had a depressed late peak filling rate, and 10 (100%) had an increased constant of myocardial stiffness. Of the 22 patients with aortic regurgitation and normal systolic function (subgroup 3a), 12 (54%) had a prolonged time constant of relaxation, none had a depressed early or late peak filling rate, but 18 (82%) had an elevated constant of myocardial stiffness. Of the 8 patients with aortic regurgitation and depressed systolic function (subgroup 3b), 6 (75%) had a prolonged time constant of LV pressure decay, none had a reduced early or late peak filling rate, but 8 (100%) had an increased constant of myocardial stiffness. A significant difference between subgroup 2a and 2b, as well as between 2a and 3a, was observed only for the constant of myocardial stiffness (Figure 4).

Diastolic dysfunction (as assessed by ≥1 abnormal index of diastolic function) was present despite normal systolic function in 9 of 18 patients (50%) with aortic stenosis (subgroup 2a) and in 20 of 22 (91%) with aortic regurgitation (subgroup 3a).

TABLE IV Indexes of Relaxation in Subgroups with Normal and Depressed Contractility

	Control Subjects (n = 11)	Aortic Stenosis 2a (n = 18)	Aortic Stenosis 2b (n = 10)	Aortic Regurgitation 3a (n = 22)	Aortic Regurgitation 3b (n = 8)
τ_d (ms)	43 ± 12	58 ± 19	84 ± 25*†	64 ± 17‡	91 ± 15*‡§
t_W (ms)	27 ± 6	32 ± 7	37 ± 7	32 ± 8	36 ± 5
t_M (ms)	29 ± 7	33 ± 8	38 ± 8	33 ± 8	36 ± 5

*p < 0.01 vs control subjects; †p < 0.01 vs 2a; ‡p < 0.05 vs 2b; §p < 0.01 vs 3a. Abbreviations as in Table II.

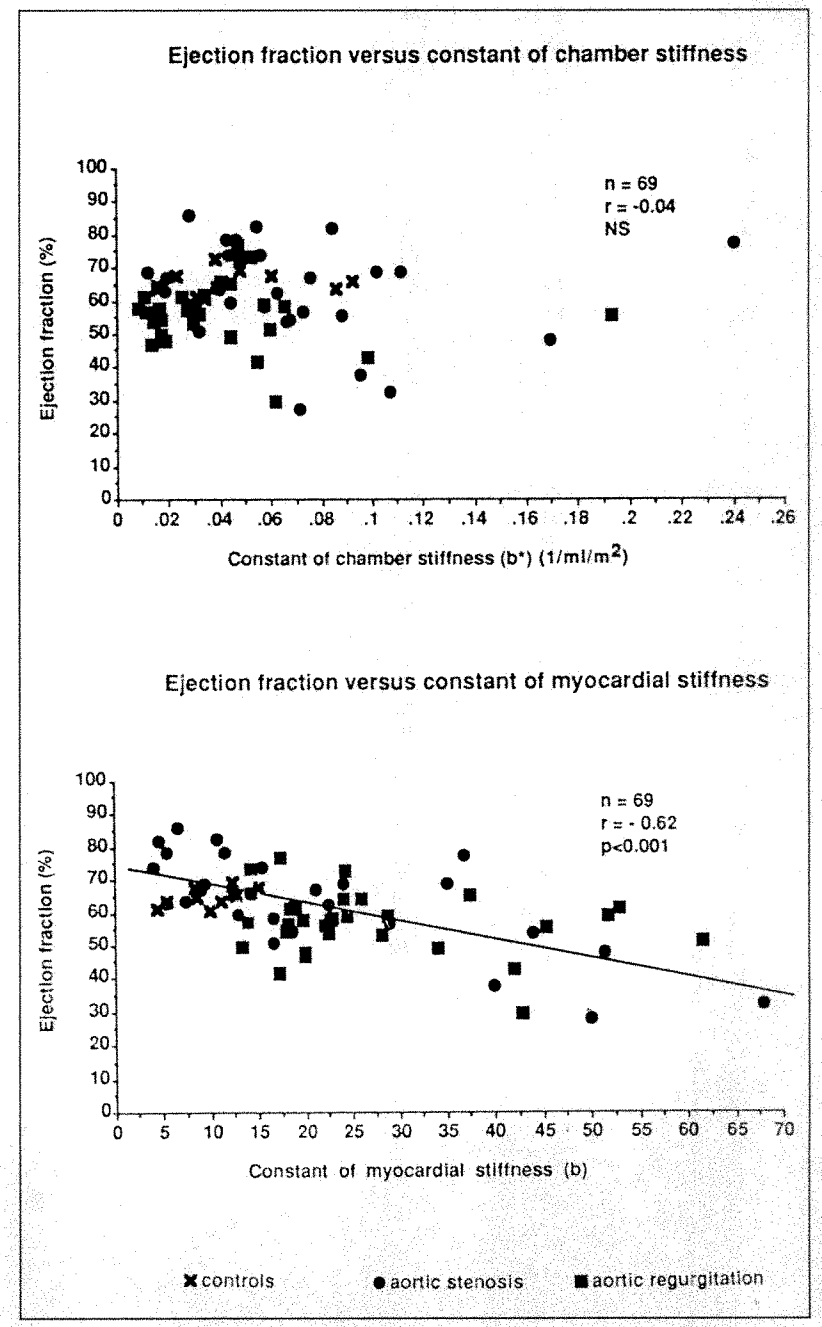


FIGURE 3. Relation between ejection fraction and passive diastolic properties. There is no relation between ejection fraction and constant of chamber stiffness, whereas there is significant (p <0.001) inverse relation between ejection fraction and constant of myocardial stiffness. NS = not significant.

TABLE V Diastolic Function in Subgroups with Normal and Depressed Contractility

		Aortic Stenosis		Aortic Regurgitation	
	Control Subjects (n = 11)	2a (n = 18)	2b (n = 10)	3a (n = 22)	3b (n = 8)
MVOP (mm Hg)	10 ± 2	18 ± 9	30 ± 12‡§§§	15 ± 8	18 ± 10
EF (%)	66 ± 4	69 ± 8	46 ± 11†‖§§	61 ± 7††	49 ± 5†‖§§
PFR1 (ml/m²/min)	269 ± 91	309 ± 105	290 ± 75‖‖	515 ± 143‡¶	336 ± 118‡‡
PFR2 (ml/m²/min)	181 ± 44	275 ± 115	185 ± 93	395 ± 219†**	400 ± 134†
b* (1/ml/m²)	0.044 ± 0.026	0.063 ± 0.041‡‡	0.083 ± 0.037*	0.033 ± 0.022**	0.058 ± 0.63
b	9.9 ± 3.3	14.2 ± 10.0	33.6 ± 17.2†§	25.3 ± 10.2*§	30.2 ± 17.0†§

*p <0.05, †p <0.01, ‡p <0.001 vs control subjects; §p <0.05, ‖p <0.01, ¶p <0.001 vs 2a; **p <0.05, ††p <0.01 vs 2b; ‡‡p <0.05, §§p <0.01, ‖‖p <0.001 vs 3a.
Abbreviations as in Tables I and II.

DISCUSSION

The effect of pressure and volume overload on ventricular function has been studied extensively, but the analysis of diastolic function in response to abnormal loading conditions has shown conflicting results, particularly during the passive filling phase. Passive elastic stiffness has been found to be normal[5] or decreased[3] in pressure or volume overload. It is possible that differences in systolic performance may account for such heterogeneity of diastolic properties; in fact, no study has directly correlated diastolic function parameters to systolic ejection performance or contractility. Moreover, only a few studies[2] analyzed separately indexes reflecting relaxation, filling and passive diastolic function. Thus, the purpose of the present study was to evaluate the relation between systolic and diastolic function in LV hypertrophy secondary to chronic overload due to aortic valve disease.

Systolic versus diastolic function: The relation between systolic and diastolic function within the framework of the hemodynamic control has been assumed to be concordant (i.e., in the presence of systolic dysfunction, diastolic function abnormalities are expected to occur, and vice versa). However, Weber[17] demonstrated in an animal model that collagen remodeling can influence systolic and diastolic properties in opposite ways. An increase in ventricular interstitial collagen was thought to increase the capability of the myocytes to generate force (preserved systolic function) by reducing the dissipation of force, and to increase diastolic stiffness (depressed diastolic function) by a direct effect of the collagen on myocardial stiffness.[5,17] Therefore, an impairment of diastolic function may precede the reduction of systolic performance.

The major findings of the present study were inverse relations between systolic ejection fraction and time constant of LV pressure decay (Figure 2), mitral valve opening pressure (Figure 2) and constant of myocardial stiffness (Figure 3). There was only a weak correlation between ejection fraction and late peak filling rate (Table III) mainly due to the large scatter in patients with aortic regurgitation. No correlation was found between ejection fraction and early peak filling rate, nor between ejection fraction and the constant of chamber stiffness

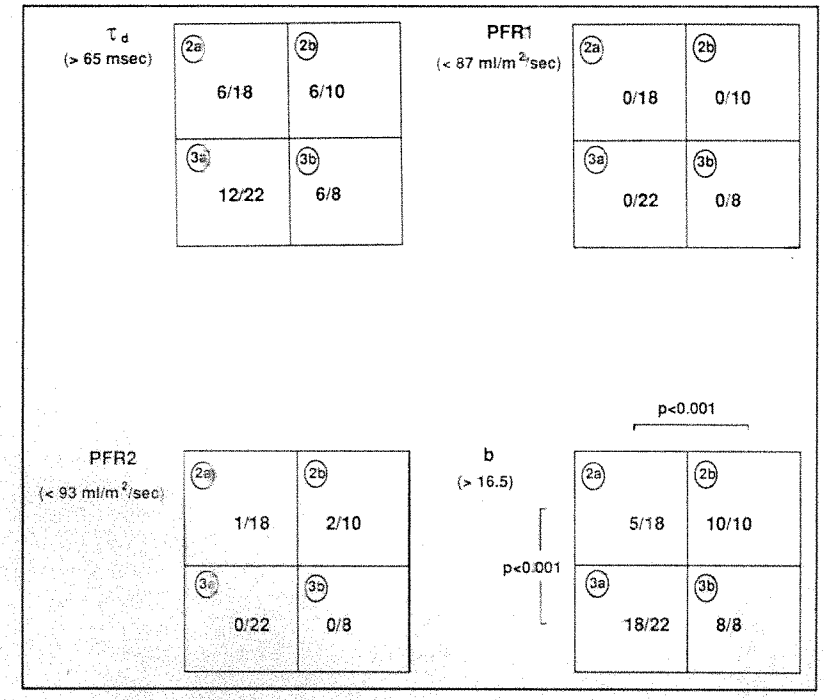


FIGURE 4. Incidence of abnormalities of evaluated parameters of diastolic function in the 4 subgroups. In patients with aortic stenosis, incidence of increased constant of myocardial stiffness (b) is lower in presence of preserved contractility (2a) than in those with depressed contractile state (2b). Incidence of increased b was also higher in aortic regurgitation (3a) than in aortic stenosis (2a) with preserved contractility. No differences between subgroups existed for time constant of left ventricular pressure decay (τ_d), and for early (PFR1) and late (PFR2) peak filling rates.

(Figure 3). Generally, a decreased ejection fraction was associated with prolonged relaxation and augmented myocardial stiffness, but diastolic abnormalities also occurred frequently in patients with normal systolic contractile function (i.e., 50% in aortic stenosis, and 91% in aortic regurgitation). Systolic dysfunction was observed in none of our patients when diastolic stiffness was normal and in 6 of 18 (33%) when relaxation was normal (Figure 4). This seems to indicate an enhanced sensitivity of passive diastolic myocardial properties and relaxation to detect functional abnormalities in patients with aortic valve disease or that these functional abnormalities precede systolic dysfunction. Peak filling rates (both early and late) did not detect any LV dysfunction, being seldom depressed in patients with unequivocal pathologic systolic function (Figure 4).

It has to be assumed that the myocardial process that is responsible for the reduction of systolic function (biochemical, humoral or structural) is also responsible for diastolic dysfunction. It has been shown that afterload mismatch[12,18] or abnormal contractile function, or both,[12,19] are responsible for the reduction of systolic ejection performance, whereas diastolic dysfunction was observed in the presence of structural alterations with increased interstitial fibrosis.[6,20] However, an inverse relation between ejection fraction and time constant of relaxation may be predictable on theoretical grounds, because ejection fraction decreases with afterload increase, whereas time constant of relaxation increases with an increase in afterload. This inverse relation has been observed in systemic hypertension.[21] Similar although less good correlations were observed between ejection fraction and t_W and t_M (Table III). Recently, Krayenbuehl et al[22] reported a close inverse relation between ejection fraction and muscle fiber diameter, but not between ejection fraction and percent interstitial fibrosis. Several studies[6,23,24] demonstrated a direct relation between interstitial fibrosis and the constant of myocardial stiffness. Ritter et al[24] demonstrated a correlation between systolic muscle stiffness constant and myocardial fiber diameter, whereas diastolic myocardial stiffness constant correlated with interstitial fibrosis, but not with muscle fiber diameter. These observations suggest that the process of ventricular hypertrophy influences both the cellular (myocyte) size and the interstitium, and leads ultimately to abnormalities in both systolic and diastolic functions.[17,23] However, this process is a dynamic one, and systolic and diastolic functional derangements may not always occur at the same time. This fact could explain the scatter of the data in the present analysis (time-dependency) (Figures 2 and 3).

Effect of pressure- and volume-overload hypertrophy: The reliability of various functional parameters as indicators for an abnormal contractile state was evaluated previously. Systolic ejection fraction was reported to be a sensitive measure for the detection of myocardial dysfunction in various pathologic states,[25,26] but this parameter is known to be afterload-dependent and thus, may be misleading in patients with aortic stenosis or regurgitation having an increased afterload. Therefore, to define the level of systolic contractile state, patients with aortic valve disease were subgrouped according to whether the shortening-afterload relation was normal or abnormal (Figure 1). In the presence of normal systolic contractility (subgroups 2a and 3a), the mean values for the time constant of relaxation and for the constant of myocardial stiffness are normal in chronic pressure, but abnormal in chronic volume overload (Tables IV and V). However, it should be noted that these indexes are abnormal in one third of patients in subgroup 2a, and also in two thirds of those in subgroup 3a (Figure 4). Why in the presence of normal contractility there is more discordance between systolic and diastolic function in chronic volume than in pressure overload is not clear and may be due to either patient selection or differences in the mechanism involved with the specific type of overload, such as eccentric versus concentric hypertrophy.[27] Recently, Corin et al[4] demonstrated a concordant behavior of systolic and diastolic function in chronic volume overload due to mitral regurgitation, attributing a major importance to the shape and the geometry of the left ventricle.

Several investigators[17,28,29] suggested that chronic volume overload is especially harmful to the ventricle, because an increased end-diastolic and end-systolic wall stress is already present in the compensated phase of chronic regurgitation. In this regard, an increased collagen fiber stretch has been reported in enlarged ventricles,[17,30] which could explain the alterations of diastolic stiffness in the presence of normal systolic contractility in patients with aortic regurgitation. Furthermore, the difference in the geometry of the ventricle could explain the higher incidence of abnormalities in myocardial passive stiffness in subgroup 3a than in 2a (Figure 4). It has been demonstrated[16] that the diastolic volume/mass ratio is a determinant of the passive elastic stiffness constant, whereby the latter tends to increase when the former is increased. In fact, subgroup 3b elicited an LV end-diastolic volume/mass ratio that was larger than that of subgroup 2a (1.10 ± 0.29 vs 0.58 ± 0.26; $p < 0.001$).

Clinical implications: Our study indicates that diastolic functional derangements can be detected frequently in patients with aortic valve disease. However, high-fidelity LV pressure measurements simultaneous with left ventriculography are mandatory for the calculation of the time constant of LV pressure decay, and the constant of myocardial stiffness (stress-strain relation). These indexes are somewhat difficult to calculate, but represent sensitive measures of diastolic ventricular dysfunction that cannot be obtained by the noninvasive techniques currently used in clinical cardiology. Echo-Doppler measurements and radionuclide angiography allow only the evaluation of filling parameters. They are not suitable methods for the detection of diastolic abnormalities occurring early in patients with aortic valve disease, because (as shown herein) diastolic filling rates are insensitive measures.

Study limitations: A reduction of LV contractility was defined in the present study by a downward displacement of the relation between systolic ejection fraction and mean systolic wall stress. Patients with aortic valve disease whose coordinates were in the 95% prediction limits of this relation were assumed to have a nor-

mal contractile state. This assumption appears to be correct as long as preload (which is another determinant of ejection fraction) is comparable to that in control subjects. In the presence of an increased preload (i.e., end-diastolic stress) but normal contractile state, the relation is shifted upward and rightward. In the absence of such a shift, a slightly reduced contractility is likely to be present when ejection fraction is kept within normal limits by the use of preload reserve. It is of interest that Krayenbuehl and Hess[26] found that 12 of 44 patients (27%) with aortic stenosis and normal ejection fraction had an abnormal relation between maximal rate of stress increase and preload, indicating a slightly depressed LV contractile state.[26] Thus, we cannot exclude that at least in some of our patients with aortic valve disease and a normal relation between ejection fraction and mean systolic wall stress, a mild depression of contractility was present that was compensated by an increase in preload. A more rigorous index of contractility may have been the end-systolic pressure-volume relation that is, however, more difficult to assess than the currently used measures. Changes in afterload may have been achieved by various interventions, but would have complicated the present evaluation and possibly only moderately improved our knowledge on the contractile state of the myocardium.

APPENDIX

Circumferential wall stress: $S = (P \cdot a/h)\ [1 - (h/2b) - (b^2/2a^2)]\ 1.322$, where S = midwall stress (kdyne/cm^2), P = LV pressure (mm Hg), h = LV wall thickness (cm), a = midwall semimajor axis, and b = midwall semiminor axis.[4]

Indexes of relaxation: (1) Time constant (τ_d): $dP/dt = -b\ (P + c)$; $\tau_d = 1/b$[14]; (2) pressure-halftime with zero asymptote: $P = a\ e^{-bt}$; $t_W = \ln[2]/b$[15]; and (3) pressure-halftime with shifting asymptote: $P = a\ e^{-bt} + c$; $t_M = [1/b]\ \ln\ [2/a-c]$,[16] where P is LV pressure, dP/dt is its first derivative, t is equal to time, and a, b and c are constants determined by linear (dP/dt) or nonlinear regression analysis.

Diastolic filling rate: $FR(t) = [V(t + 20) - V(t - 20)]/0.04$, where t is equal to time, and V to volume.[2]

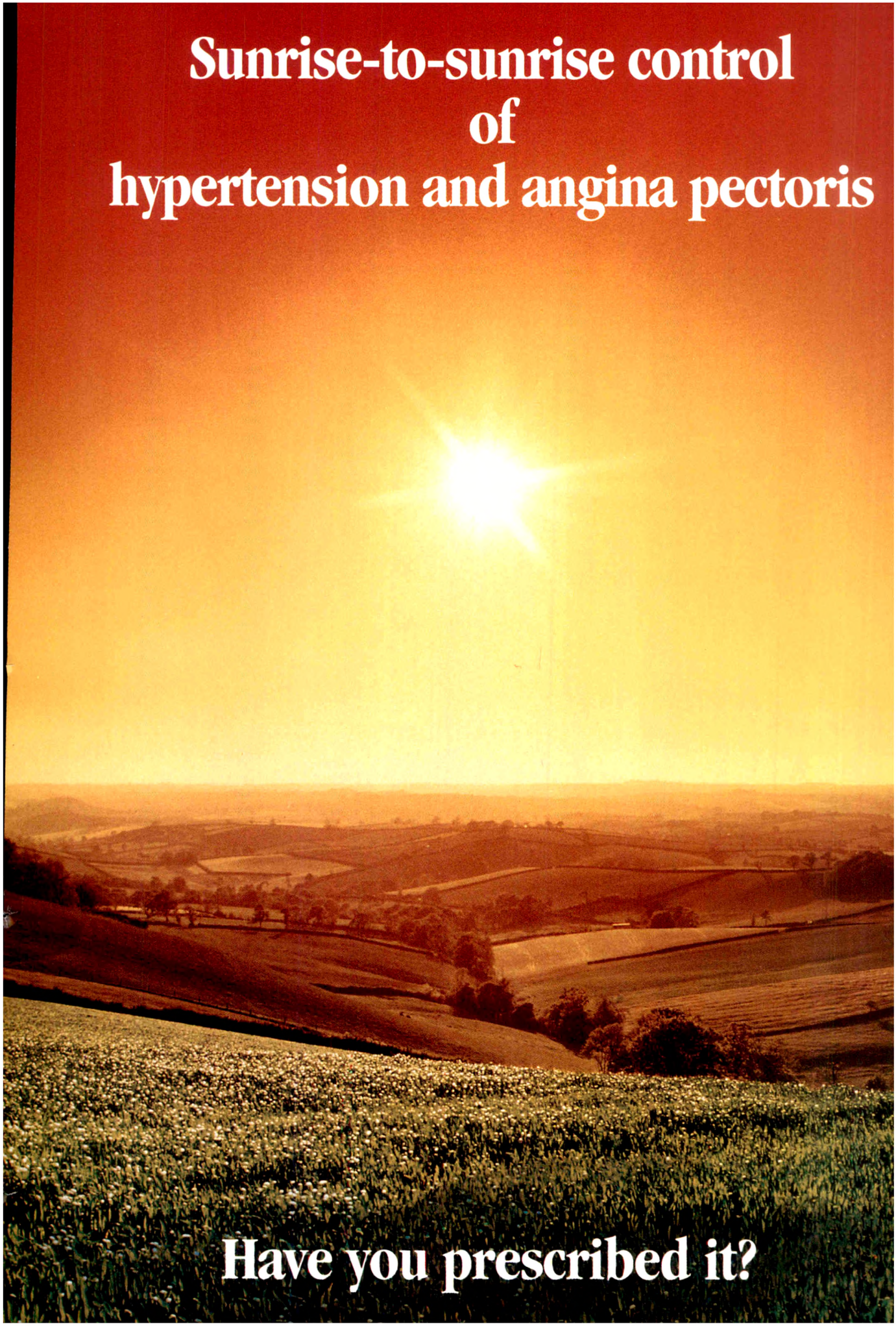
Passive elastic properties: Pressure-volume data: $P = a^* e^{b^*V} + c^*$, where P = LV pressure (mm Hg), a* = elastic constant (mm Hg), b* = constant of LV chamber stiffness (1/ml/m^2), V = LV volume (ml/m^2), and c* = asymptote of the exponential pressure-volume relation (mm Hg).[4]

Normalized pressure-volume data: $P = a' e^{b'(V/Vw)} + c'$, where Vw = wall volume (ml/m^2) (other abbreviations as in pressure-volume data).

Stress-strain data: $S = ae^{b\epsilon} + c$, where S = LV circumferential wall stress (kdyne/cm^2), a = elastic constant (kdyne/cm^2), b = constant of myocardial stiffness, ϵ = Lagrangian strain, and c = asymptote of the stress-strain relation (kdyne/cm^2).[4]

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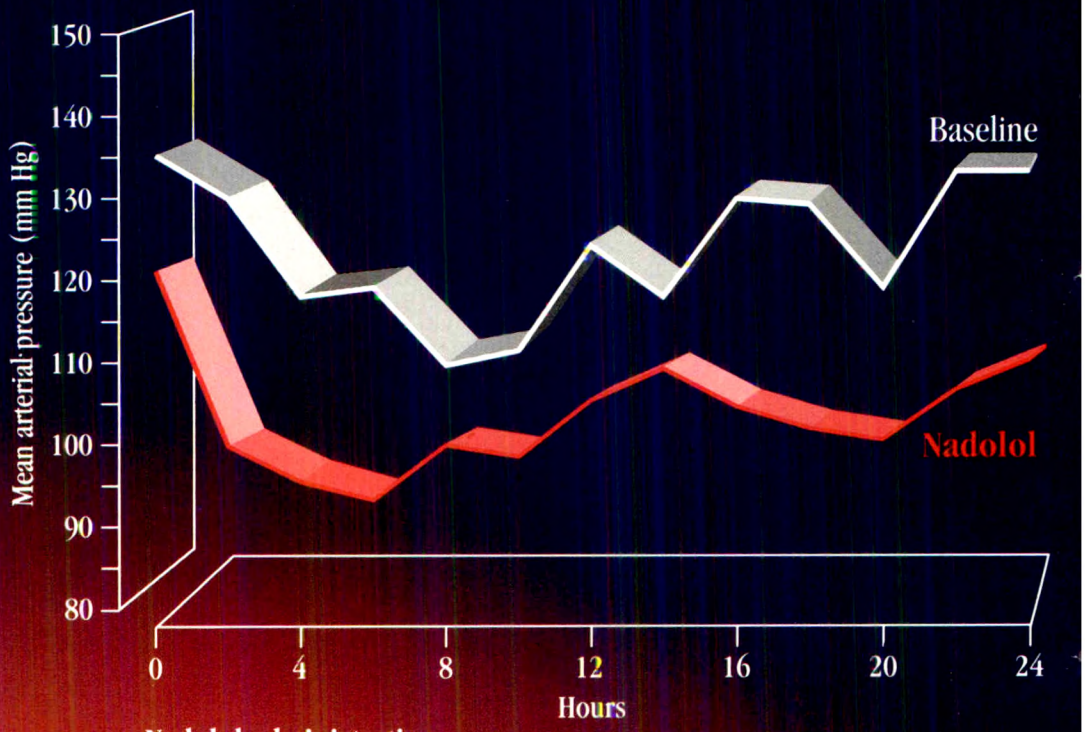

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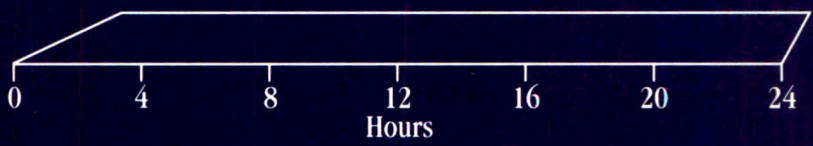
Nadolol administration

24-Hour data from 7 hypertensive patients.
Nadolol doses 80 mg to 320 mg QD.

– Adapted from Mancia G, et al.[1]

✓ angina pectoris[2]

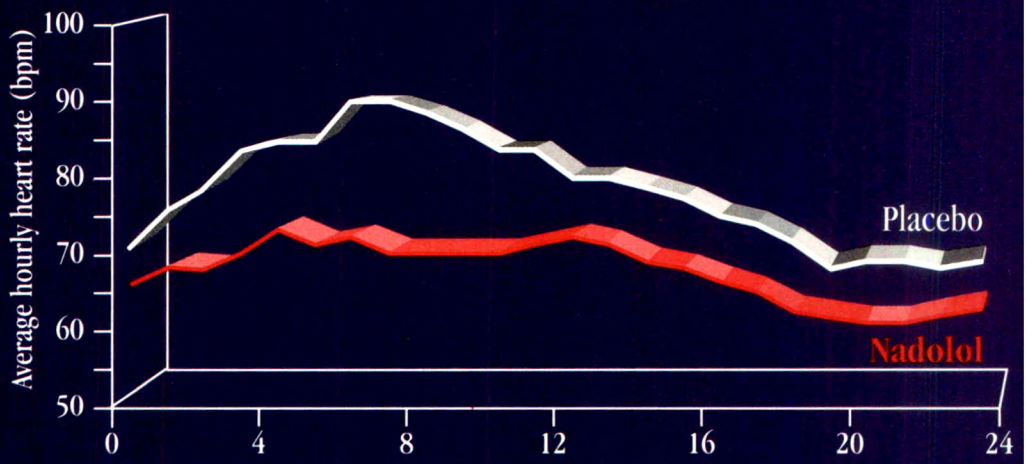
Efficacy established at 3 hours . . . maintained at 24 hours



Eighteen patients were tested on treadmill at 3 and 24 hours after ingestion of nadolol (40-160 mg QD).

– Adapted from Kostis JB, et a

heart rate[3]



Randomized, double-blind, placebo-controlled, crossover study in 16 patients with effort angina. Mean dosing time nadolol: 9:36 AM.

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CORGARD® *(nadolol)* *40 mg tablets*

True ***Sunrise-to-sunrise contro***

Please see brief summary of prescribing information on adjacent page

CORGARD® TABLETS
Nadolol Tablets USP

DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure–Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal–Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)–PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery–Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart-beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia–Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis–Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function–Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients–Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions–Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)–hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (eg, reserpine)–additive effect; monitor closely for hypotension and/or excessive bradycardia.

Response to Treatment for Anaphylactic Reaction–While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility–In 1- to 2-year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C–In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturition have exhibited bradycardia, hypoglycemia, and associated symptoms.

Nursing Mothers–Nadolol is excreted in human milk. Exercise caution when nadolol is administered to a nursing woman.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular–Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**–Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**–Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**–Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**–Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/or other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**–reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**–mesenteric arterial thrombosis; ischemic colitis; elevated liver enzymes. **Hematologic**– agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**–fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**–pemphigoid rash; hypertensive reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia–Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure–Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension–Administer vasopressors, eg, epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm–Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE–For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses up to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles of 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

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Convenient once-daily dosing



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References:

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Clinical Course of Middle-Aged Asymptomatic Patients with Hypertrophic Cardiomyopathy

Gabriela M. Hecht, MD, Julio A. Panza, MD, and Barry J. Maron, MD

Patients with hypertrophic cardiomyopathy (HC) may present a wide spectrum of clinical and morphologic manifestations. Although many aspects of the natural history of HC are understood, the initial presentation and subsequent clinical course of certain subgroups are not yet well defined. To further our understanding in this regard, 241 middle-aged patients with HC (aged 35 to 55 years) were analyzed. The vast majority of patients (210) had already experienced symptoms, whereas the remaining 31 initially presented with no or minimal symptoms and are the focus of this investigation; 29 of these were followed for ≥2 years (range to 11.5 years, mean 8). A separate group of 30 moderately symptomatic age- and gender-matched patients with HC were selected as control subjects for morphologic comparisons.

Of the 29 study patients with follow-up, 22 (76%) are presently free of important cardiac symptoms, but 3 showed progression of symptoms, and 4 have died suddenly. Annual mortality rate was 1.7%. Eighteen of the middle-aged asymptomatic patients with HC (58%) had localized left ventricular hypertrophy, usually involving only the anterior ventricular septum; in contrast, only 9 of the 30 symptomatic control subjects (30%) had such localized hypertrophy ($p = 0.02$).

In conclusion, of those patients with HC who achieved middle-age without developing important cardiac symptoms, approximately 75% remained asymptomatic during the ensuing average 8-year follow-up. However, such patients are not protected in absolute terms from unfavorable clinical events (despite relatively mild left ventricular hypertrophy and in most cases absence of outflow obstruction). This is evidenced by the fact that approximately 25% eventually experienced symptomatic deterioration or sudden cardiac death.

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Hypertrophic cardiomyopathy (HC) is a primary cardiac disease characterized by heterogeneity in its clinical and morphologic manifestations.[1–15] The natural history of this disease ranges widely from patients who remain relatively asymptomatic throughout their natural lives to those who experience premature unexpected sudden cardiac death or progressive cardiac failure at various ages.[16–30]

This diversity in HC has been an impediment to our understanding of the natural history, prognosis and morphologic features of all subsets of patients within the broad disease spectrum. It was our impression, however, that some patients achieved mid-life without incurring symptoms and appeared to have a clinically benign form of the disease. Therefore, in the present study, we focused our attention on this selected subgroup of asymptomatic middle-aged patients with HC in order to define their subsequent outcome, as well as the potential morphologic determinants of their clinical course.

METHODS

Selection of patients: The case records of the echocardiography laboratory of the National Heart, Lung, and Blood Institute were reviewed from February 1979 to June 1985. During this time period, 241 middle-aged nonoperated patients with HC (aged 35 to 55 years), free of associated cardiac disease, underwent initial evaluation at our institution, including combined M-mode and 2-dimensional echocardiographic examination. Of these 241 patients, 210 presented with moderate to severe symptoms (Table I) (New York Heart Association functional class II–IV) and were therefore excluded from the analysis. The remaining subgroup of 31 asymptomatic patients with HC (aged 35 to 55 years when first evaluated at our institution) represent the focus of the present study. The 210 patients with and 31 without symptoms did not differ significantly with regard to gender and presence of left ventricular outflow obstruction under basal conditions, although the symptomatic patients were older than the asymptomatic patients (Table I).

The diagnosis of HC was based on the demonstration of a hypertrophied, nondilated left ventricle in the absence of another cardiovascular or systemic disease that could itself produce left ventricular hypertrophy of the magnitude present in that patient.[31] Eight study patients had history of relatively mild, intermittent increases in systemic blood pressure (<150/100 mm Hg). However, in each of these patients, the presence of HC was supported by other clinical or morphologic features of the disease (e.g., documented family history of HC,

TABLE I Comparison of Asymptomatic and Symptomatic Middle-Aged Patients with Hypertrophic Cardiomyopathy

	Asymptomatic	Symptomatic	p Value
No. of pts.	31	210	—
Mean age (yr) (range)	42 ± 5 (35–55)	46 ± 6 (35–55)	<0.0001
Men (%)	25 (81)	139 (66)	NS
Functional class*			
I	31	0	—
II	0	80	—
III	0	96	—
IV	0	34	—
No. of pts. with basal LV outflow obstruction (cardiac catheterization)	3/7	62/128	NS

*Functional class at initial evaluation.
LV = left ventricular; NS = nonsignificant; — = data not applicable.

unusual distribution of segmental left ventricular hypertrophy, or magnitude of wall thickening clearly exceeding that which could reasonably be expected to occur secondary to mild systemic hypertension).[32]

A separate group of 30 consecutive patients with HC and moderate symptoms (functional class II) were chosen as age- and sex-matched control subjects solely for the purpose of obtaining selected morphologic and hemodynamic comparisons with the 31 asymptomatic study patients; this group did not serve as control subjects with regard to clinical outcome.

Echocardiography: Echocardiographic examinations were performed using a commercially available phased array or mechanical sector scanning echocardiographic instrument with 2.25 or 3 MHz transducers; images were recorded on 3/4-inch videotape. M-mode echocardiograms were derived from the 2-dimensional image under direct anatomic visualization. Cardiac dimensions were assessed from the M-mode echocardiogram according to the criteria of the American Society of Echocardiography.[33]

Two-dimensional echocardiographic studies were obtained in the parasternal long- and short-axis, and apical views using standard transducer positions.[34] Distribution and extent of left ventricular hypertrophy was assessed from the 2-dimensional echocardiogram, as previously described.[35] In the short-axis view, the left ventricle was divided in 4 segments, and measurements of wall thickness were obtained in each of these regions. Maximal wall thickness was defined in each patient as the greatest thickness identified in any of the 4 segments in which the left ventricle had been divided.

The extent of left ventricular hypertrophy was categorized according to the number of segments involved[36]: localized (1 segment), intermediate (2) and diffuse (3 or 4). In the 7 study patients who underwent cardiac catheterization, obstruction to left ventricular outflow was defined as a basal gradient ≥30 mm Hg. In the 24 patients who did not undergo cardiac catheterization, subaortic obstruction was assessed by the magnitude and duration of systolic anterior motion of the mitral valve on the M-mode echocardiogram.[37,38]

Statistical methods: Data were expressed as mean ± SD. Differences between means were analyzed using the unpaired Student's *t* test. Differences between proportions were assessed using chi-square or 1-tailed Fisher's exact test.

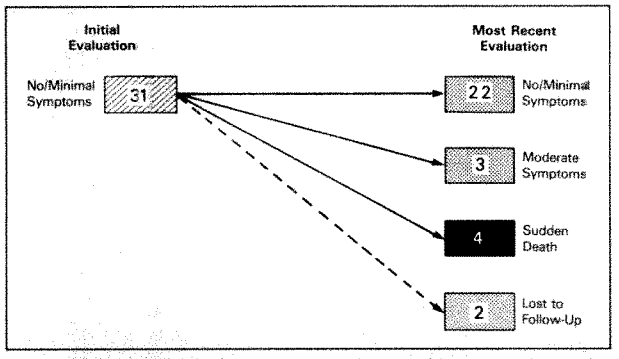


FIGURE 1. Clinical outcome in 31 asymptomatic middle-aged patients with hypertrophic cardiomyopathy assessed over mean follow-up of 8 years (range 2.1 to 11.5).

RESULTS

Clinical findings and natural history: By selection, all 31 study patients (mean age 41.6 ± 5 years, range 35 to 55; 25 men [81%]) were virtually asymptomatic at their initial evaluation. Clinical course could be assessed for ≥2 years after initial evaluation in 29 patients; follow-up ranged to 11.5 years (mean 8) (Figure 1). During follow-up, 22 (76%) patients remained completely asymptomatic or had only minor and transient symptoms. Three patients had an increase in symptoms (1 to functional class II, and 2 to class III).

The remaining 4 patients (3 men and 1 woman) died suddenly; the annual mortality rate was 1.7% (Table II). The first of these patients survived cardiac arrest at age 50 while being treated with amiodarone, but died 3 months later of uncontrolled ventricular tachyarrhythmias during a map-guided ventricular tachycardia ablation procedure. The other 3 patients died during sedentary activities. One patient with history of paroxysmal atrial fibrillation died suddenly at age 51 and 2 patients were virtually asymptomatic before death at ages 55 and 64 years, respectively. In 3 of the 4 patients who died suddenly, coronary arteriography had been performed at the first evaluation or during follow-up and showed absence of coronary artery disease; none had a necropsy examination.

Medications: Eighteen of the 29 study patients who were followed longitudinally received clinically appropriate dosages of cardioactive medications (i.e., β blockers or verapamil) for more than one half of the follow-up period; these drugs were administrated either prophylactically[29] or for symptoms that developed. Five of these 18 patients also received primary antiarrhythmic medications (procainamide, quinidine or amiodarone) for atrial fibrillation or ventricular arrhythmias identified by ambulatory electrocardiogram. Eleven other patients either did not receive cardiac medications or did so for only abbreviated periods of time.

TABLE II Clinical and Morphologic Data in the Four Middle-Aged Asymptomatic Patients with Hypertrophic Cardiomyopathy Who Died Suddenly

Pt.	Age (yr) at Death & Sex	FC	Symptoms at Last Evaluation	Follow-Up (mos)	Max. LV Thickness (mm)	Extent of LVH*	Arrhythmia		LVOT Gradient (mm Hg)†	CAD	Circumstances at Death	Medications
							VT	Other				
1	50M	II	Syncope	25	23	Intermediate	+	0	0	0‡	Ablation§	Amiodarone; atenolol
2	51M	II	Palpitations; DOE	36	20	Diffuse	0	PAF	60	0‖	Sedentary	Amiodarone; verapamil
3	55F	II	Palpitations; lightheadedness	136	18	Intermediate	0	0	55	0¶	Sedentary	Propranolol
4	64M	I	Palpitations	131	18	Localized	+	0	0	—	Sedentary	Procainamide; atenolol

*Localized: involvement of 1 LV segment; intermediate: involvement of 2 LV segments; diffuse: involvement of 3 or 4 LV segments.
†Measured at cardiac catheterization or estimated from M-mode echocardiogram.[37,38]
‡Coronary arteriography performed 9 months before death.
§Patient died during map-guided ventricular tachycardia ablation procedure.
‖Coronary arteriography performed 3 years before death.
¶Coronary arteriography performed 11 years before death.
CAD = coronary artery disease; DOE = dyspnea on exertion; FC = functional class (New York Heart Association) before death; LV = left ventricle; LVH = left ventricular hypertrophy; LVOT = left ventricular outflow tract; Max. = maximum; PAF = paroxysmal atrial fibrillation; VT = ventricular tachycardia; — = data not obtained.

When the 4 patients who died suddenly were analyzed separately, it was determined that 3 had received antiarrhythmic medications during the year before death (Table II); 1 with atrial fibrillation was treated with amiodarone, and 2 with sustained or nonsustained ventricular tachycardia received either amiodarone or procainamide. Three of these 4 patients also received β blockers, and the other was taking verapamil.

Distribution and extent of hypertrophy: Maximum left ventricular wall thickness in the asymptomatic middle-aged patients with HC ranged from 14 to 30 mm (mean 19.5 ± 4) (Figure 2). The majority of these patients (23 of 31) had a maximum wall thickness that ranged between 14 and 20 mm (Figure 2); 4 patients had markedly increased wall thickness (i.e., 28 to 30 mm).

Analysis of extent and distribution of hypertrophy in the 31 asymptomatic study patients showed that 18 (58%) had increased wall thickening localized to 1 segment of the left ventricular wall (Figure 3). In these 18 patients, hypertrophy was confined to the basal anterior ventricular septum in 13 (Figure 4), distal anterior septum in 3, and posterior septum in 2. The remaining 13 patients (42%) had left ventricular hypertrophy that involved >1 segment; in 7 patients, 2 segments were thickened, whereas in the other 6 patients the pattern of hypertrophy was diffuse (involving 3 or 4 segments). Of the 4 patients who died suddenly, 1 had diffuse, 1 had localized and 2 had an intermediate degree of wall thickening (involving 2 segments). Maximum left ventricular wall thickness in the 4 patients who died suddenly (19.7 ± 2 mm) did not differ from that of the 25 surviving patients with follow-up (19.4 ± 5 mm; Figure 2).

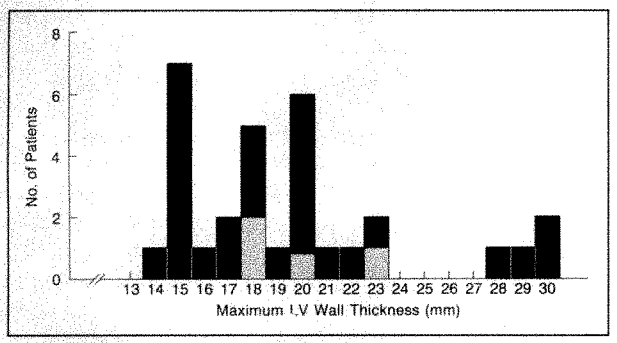


FIGURE 2. Maximum left ventricular (LV) wall thicknesses in 31 asymptomatic middle-aged patients with hypertrophic cardiomyopathy. Four patients who ultimately died suddenly are depicted by *stippled portions* of appropriate *bars*.

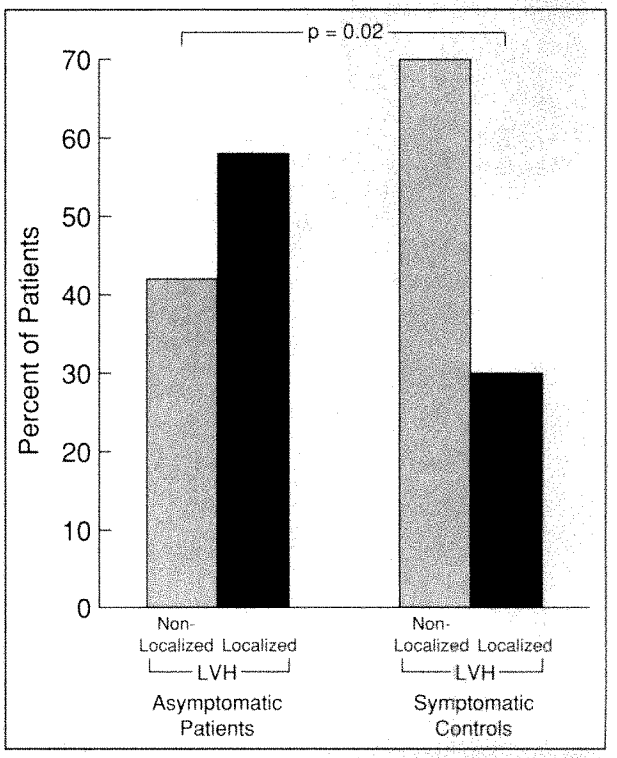


FIGURE 3. Extent of left ventricular hypertrophy (LVH) in 31 asymptomatic middle-aged patients and 30 age- and sex-matched symptomatic control subjects with hypertrophic cardiomyopathy.

In contrast, only 9 of the 30 control patients (30%) with moderate symptoms had hypertrophy localized to 1 left ventricular segment ($p = 0.02$); the remaining 21 (70%) had nonlocalized hypertrophy (involving 2 segments in 11 patients, and 3 to 4 segments in 10 patients). Wall thickness in the asymptomatic study patients was similar to that in the 30 symptomatic controls (19.5 ± 4 vs 21.7 ± 4 mm; p = not significant).

Obstruction to left ventricular outflow: Based on combined echocardiographic and hemodynamic data, 22 of the 31 asymptomatic patients (71%) did not have evidence of obstruction to left ventricular outflow under basal conditions. Similarly, most control patients with symptoms (23 of 30, 77%) also did not have outflow obstruction (p = not significant). Of the 4 patients who died suddenly, 2 had evidence of obstruction to left ventricular outflow under basal conditions, and the other 2 did not.

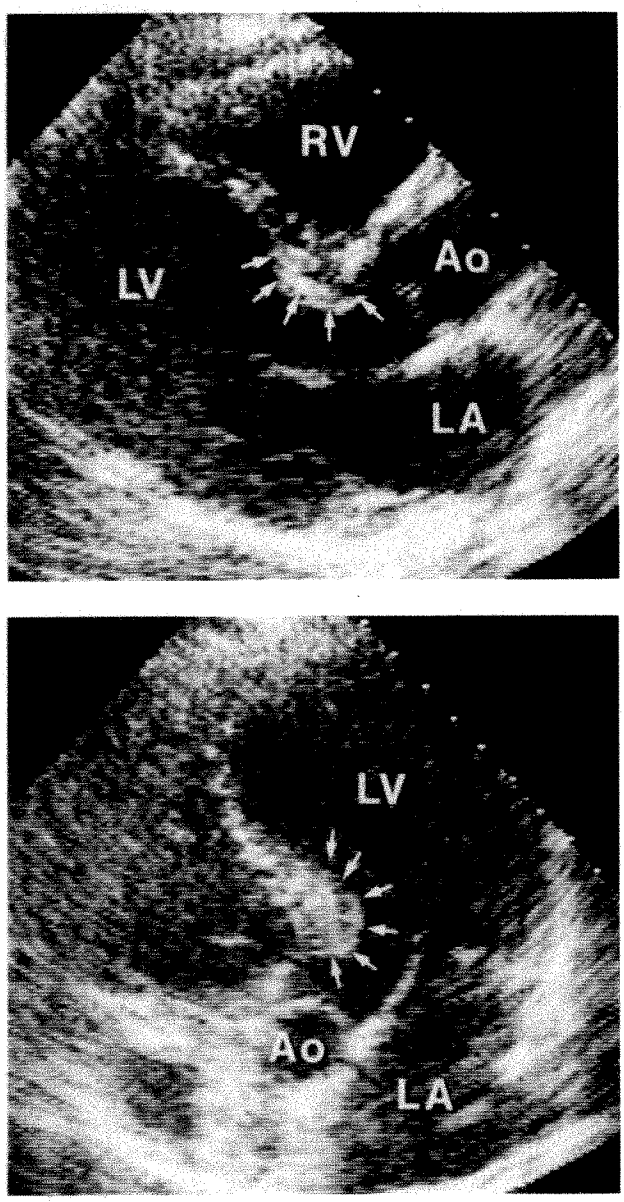


FIGURE 4. Two-dimensional echocardiogram from a 43-year-old man with nonobstructive hypertrophic cardiomyopathy shown in parasternal long-axis view *(top)*, and apical view rotated to image left ventricular outflow tract and aortic root *(bottom)*. Left ventricular hypertrophy is relatively mild and confined to anterior basal ventricular septum *(arrowheads)*, which is 17 mm in thickness *(arrows)*. *Calibration dots* are 1 cm apart. Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.

Electrocardiographic findings: Electrocardiograms recorded at the initial evaluation were abnormal in 27 of the 31 study patients (90%). A variety of electrocardiographic abnormalities were identified; most frequent were ST-segment and T-wave alterations (23 patients), left ventricular hypertrophy (Romhilt-Estes score ≥ 5 points; 18 patients)[39] and pathologic Q waves (15 patients). Other abnormalities included left atrial enlargement (10 patients), right atrial enlargement (5) and conduction abnormalities (10; first-degree atrioventricular block in 8, and left anterior fascicular block in 2). Electrocardiographic patterns did not appear to differ substantially between the 4 patients who died suddenly and the 25 surviving patients with follow-up.

DISCUSSION

Most previous investigations of the natural history of HC analyzed large heterogeneous hospital-based patient populations.[2-4,8,9,11,12,14] Such studies demonstrated that the clinical course of HC is highly variable, although many patients may develop symptoms or experience sudden death relatively early in life; the annual mortality rate has been reported to be approximately 2 to 4%.[3,4,12,26,40]

In the present study, we attempted to define the clinical course of a particular subgroup of patients with HC, i.e., those who had reached middle-age (arbitrarily defined as age 35 years) without developing significant symptoms. The reason we decided to focus on this issue is that it was our clinical impression that those patients with HC who had already achieved mid-life without incurring important cardiac symptoms or clinical events may represent a subgroup that had been, through time, selected for a relatively benign life-long clinical course. However, our data analysis did not prove this assumption to be correct. Although most of our middle-aged asymptomatic patients remained stable and did not incur important symptoms during the subsequent 8-year follow-up, approximately 25% developed progressive symptoms or died suddenly. The annual mortality rate for our patient group (approximately 2%) did not differ substantially from that previously reported in other groups with HC, not limited to patients aged >35 years[3-5,8,12]; moreover, the 4 deaths in the present study occurred between ages 50 and 65, a period of life often perceived to be beyond the greatest risk for such catastrophes in patients with HC.[2-4,10-12,17,21] Hence, particularly long periods of clinical stability may nevertheless be followed later in life by adverse events (including sudden cardiac death). Indeed, the 210 middle-aged symptomatic patients with HC (originally surveyed for inclusion in the present study) proved to be somewhat older than the 31 asymptomatic study patients, suggest-

ing that the latter may yet experience disease progression as they grow older.

Our observations in middle-aged patients with HC are probably relevant to those patients who have been described as representing the stable asymptomatic segment of the HC population (i.e., those not often referred to tertiary centers for diagnosis and management of high-risk circumstances).[16,22] Spirito et al[16] emphasized that an outpatient population with HC may have a much more benign natural history, and therefore represents a mild clinical expression within the broad HC disease spectrum. Our data support the premise that such asymptomatic patients with HC are seldom referred to centers such as the National Institutes of Health (indeed, they constituted <15% of our consecutive group of 241 patients with HC). However, in contrast to Spirito et al,[16] our findings in mid-life patients suggest that the clinical course of this segment of the HC population is perhaps not as innocent as previously thought and that these patients remain at enhanced risk later in life.

Unfortunately, in 2 of our 4 patients who died suddenly, the presence of associated coronary artery disease could not be excluded definitively (in 1 because coronary arteriography was not performed, and in the other because it was performed 11 years before death). However, the fact that neither patient had ever experienced chest pain at least suggests that clinically relevant atherosclerotic coronary disease may well have been absent.

It has been inferred that a relatively mild morphologic expression and absence of left ventricular outflow obstruction may be associated with a more favorable clinical course in HC.[41,42] Indeed, echocardiographic studies in our 31 asymptomatic study patients more frequently showed localized patterns of left ventricular hypertrophy than did an age- and sex-matched symptomatic control group with this disease (although maximum left ventricular wall thickness did not differ significantly between these groups). However, it should also be noted that 3 of our 4 patients who died suddenly had relatively mild increases in left ventricular wall thickness, suggesting that older patients with HC and mild hypertrophy are probably not preferentially protected from sudden cardiac death.

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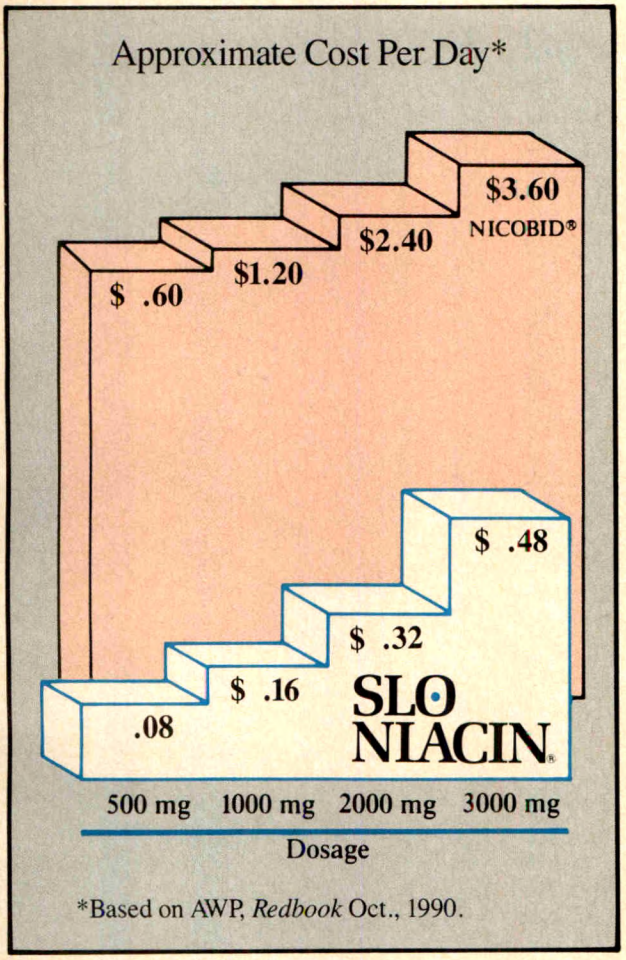
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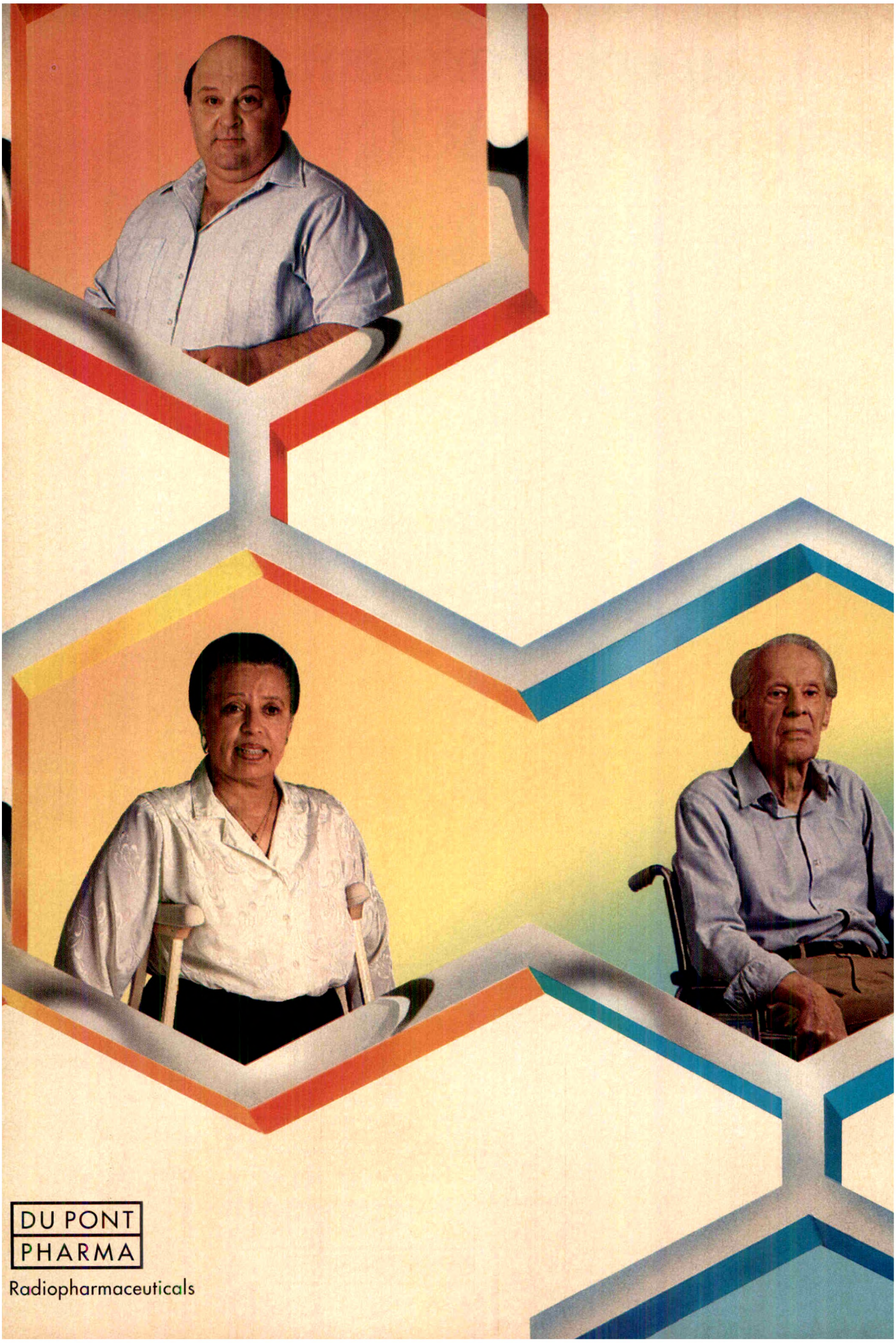
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Thallium Tl 201 is cyclotron produced with no carrier added and contains no less than 98% Thallium Tl 201 as a percentage of total activity with contaminants less than 0.3% Thallium Tl 200, 1.2% Thallium Tl 202, and 0.2% Lead Pb 203 expressed as a percentage of Tl 201 activity at calibration.
It is recommended that Thallous Chloride Tl 201 be administered close to calibration time to minimize the effect of higher levels of radionuclide contaminant.

INDICATIONS AND USAGE: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction. It may also have prognostic value regarding survival, when used in the clinically stable patient following the onset of symptoms of an acute myocardial infarction, to assess the site and size of the pertusion defect.
Thallous Chloride Tl 201 may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).
It is usually not possible to differentiate recent from old myocardial infarction, or to differentiate exactly between recent myocardial infarction and ischemia.
Thallous Chloride Tl 201 is indicated also for the localization of sites of parathyroid hyperactivity in patients with elevated serum calcium and parathyroid hormone levels. It may also be useful in pre-operative screening to localize extrathyroidal and mediastinal sites of parathyroid hyperactivity and for post-surgical reexamination. Thallous Chloride Tl 201 has not been adequately demonstrated to be effective for the localization of normal parathyroid glands.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

PRECAUTIONS: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of Thallous Chloride Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

GENERAL: Do not use after the expiration time and date (5 days maximum after calibration time) stated on the label.
Do not use if contents are turbid.
The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.
Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.
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Pediatric Use: Safety and effectiveness in children below the age of 18 have not been established
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Prescribing Information **For Intravenous Injection**

INDICATIONS AND USAGE IV Persantine® (dipyridamole USP) is indicated as an alternative to exercise in thallium myocardial perfusion imaging for the evaluation of coronary artery disease in patients who cannot exercise adequately.

CONTRAINDICATIONS Hypersensitivity to dipyridamole.

WARNINGS Serious adverse reactions associated with the administration of intravenous Persantine® (dipyridamole USP) have included fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, transient cerebral ischemia, and bronchospasm.
In a study of 3911 patients given intravenous Persantine as an adjunct to thallium myocardial perfusion imaging, two types of serious adverse events were reported: 1) four cases of myocardial infarction (0.1%), two fatal (0.05%); and two non-fatal (0.05%); and 2) six cases of severe bronchospasm (0.2%). Although the incidence of these serious adverse events was small (0.3%,10 of 3911), the potential clinical information to be gained through use of intravenous Persantine thallium imaging (see Indications and Usage noting the rate of false positive and false negative results) must be weighed against the risk to the patient. Patients with a history of unstable angina may be at a greater risk for severe myocardial ischemia. Patients with a history of asthma may be at a greater risk for bronchospasm during IV Persantine use.
When thallium myocardial perfusion imaging is performed with intravenous Persantine, parenteral aminophylline should be readily available for relieving adverse events such as bronchospasm or chest pain. Vital signs should be monitored during, and for 10-15 minutes following, the intravenous infusion of Persantine and an electrocardiographic tracing should be obtained using at least one chest lead.
Should severe chest pain or bronchospasm occur, parenteral aminophylline may be administered by slow intravenous injection (50-100 mg over 30-60 seconds) in doses ranging from 50 to 250 mg. In the case of severe hypotension, the patient should be placed in a supine position with the head tilted down if necessary, before administration of parenteral aminophylline. If 250 mg of aminophylline does not relieve chest pain symptoms within a few minutes, sublingual nitroglycerin may be administered. If chest pain continues despite use of aminophylline and nitroglycerin, the possibility of myocardial infarction should be considered. If the clinical condition of a patient with an adverse event permits a one minute delay in the administration of parenteral aminophylline, thallium-201 may be injected and allowed to circulate for one minute before the injection of aminophylline. This will allow initial thallium perfusion imaging to be performed before reversal of the pharmacologic effects of Persantine on the coronary circulation.

PRECAUTIONS See WARNINGS.
Drug Interactions Oral maintenance theophylline may abolish the coronary vasodilatation induced by intravenous Persantine® (dipyridamole USP) administration. This could lead to a false negative thallium imaging result.
Carcinogenesis, Mutagenesis, Impairment of Fertility In studies in which dipyridamole was administered in the feed at doses of up to 75 mg/kg/day (9.4 times* the maximum recommended daily human oral dose) in mice (up to 128 weeks in males and up to 142 weeks in females) and rats (up to 111 weeks in males and females) there was no evidence of drug related carcinogenesis. Mutagenicity tests of dipyridamole with bacterial and mammalian cell systems were negative. There was no evidence of impaired fertility when dipyridamole was administered to male and female rats at oral doses up to 500 mg/kg/day (63 times* the maximum recommended daily human oral dose). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg/day.
*Calculation based on assumed body weight of 50 kg.
Pregnancy Category B Reproduction studies performed in mice and rats at daily oral doses of up to 125 mg/kg (15.6 times* the maximum recommended daily human oral dose) and in rabbits at daily oral doses of up to 20 mg/kg (2.5 times* the maximum recommended daily human oral dose) have revealed no evidence of impaired embryonic development due to dipyridamole. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.
*Calculation based on assumed body weight of 50 kg.
Nursing Mothers Dipyridamole is excreted in human milk.
Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS Adverse reaction information concerning intravenous Persantine® (dipyridamole USP) is derived from a study of 3911 patients in which intravenous Persantine was used as an adjunct to thallium myocardial perfusion imaging and from spontaneous reports of adverse reactions and the published literature.
Serious adverse events (fatal and non-fatal myocardial infarction, severe ventricular arrhythmias, and serious CNS abnormalities) are described above (see WARNINGS).
In the study of 3911 patients, the most frequent adverse reactions were: chest pain/angina pectoris (19.7%), electrocardiographic changes (most commonly ST-T changes) (15.9%), headache (12.2%), and dizziness (11.8%).
Adverse reactions occurring in greater than 1% of the patients in the study are chest pain/angina pectoris (19.7%), headache (12.2%), dizziness (11.8%), electrocardiographic abnormalities/ST-T changes (7.5%), electrocardiographic abnormalities/extrasystoles (5.2%), hypotension (4.6%), nausea (4.6%), flushing (3.4%), electrocardiographic abnormalities/tachycardia (3.2%), dyspnea (2.6%), pain unspecified (2.6%), blood pressure lability (1.6%), hypertension (1.5%), paresthesia (1.3%), fatigue (1.2%).
Less common adverse reactions occurring in 1% or less of the patients within the study included:
Cardiovascular System: Electrocardiographic abnormalities unspecified (0.8%), arrhythmia unspecified (0.6%), palpitation (0.3%), ventricular tachycardia (0.2% see WARNINGS), bradycardia (0.2%), myocardial infarction (0.1% see WARNINGS), AV block (0.1%), syncope (0.1%), orthostatic hypotension (0.1%), atrial fibrillation (0.1%), supraventricular tachycardia (0.1%), ventricular arrhythmia unspecified (0.03% see WARNINGS), heart block unspecified (0.03%), cardiomyopathy (0.03%), edema (0.03%).
Central and Peripheral Nervous System: Hypothesia (0.5%), hypertonia (0.3%), nervousness/anxiety (0.2%), tremor (0.1%), abnormal coordination (0.03%), somnolence (0.03%), dysphonia (0.03%), migraine (0.03%), vertigo (0.03%).
Gastrointestinal System: Dyspepsia (1.0%), dry mouth (0.8%), abdominal pain (0.7%), flatulence (0.6%), vomiting (0.4%), eructation (0.1%), dysphagia (0.03%), tenesmus (0.03%), appetite increased (0.03%).
Respiratory System: Pharyngitis (0.3%), bronchospasm (0.2% see WARNINGS), hyperventilation (0.1%), rhinitis (0.1%), coughing (0.03%), pleural pain (0.03%).
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Comparison of Magnetic Resonance Imaging with Cross-Sectional Echocardiography in the Assessment of Left Ventricular Mass in Children Without Heart Disease and in Aortic Isthmic Coarctation

Michael Vogel, MD, Heiko Stern, MD, Richard Bauer, MD, and Konrad Bühlmeyer, MD

Although left ventricular (LV) mass may be important to judge effects of left-sided cardiac obstruction or hypertension, reproducible noninvasively determined normal data in the pediatric age group are scarce. To validate cross-sectional echocardiographic LV mass determination, our data were compared with LV mass assessed by magnetic resonance imaging (MRI). MRI was considered to be a good reference method because there is usually no problem in defining endo- and epicardial borders with MRI. LV mass was assessed in 14 children aged 5.3 years (10 days to 14.7 years) with a mean body surface area of 0.78 m^2 (range 0.25 to 1.61). With cross-sectional echocardiography the epicardial and endocardial volumes were calculated using a Simpsons rule algorithm in the apical 2- and 4-chamber view. The difference between epi- and endocardial volumes was multiplied by 1.05 to yield the mass. Mass was assessed with MRI using a multislice technique; the area of each myocardial slice was calculated and multiplied with the slice thickness, and the resultant slice volumes were added to obtain the myocardial volume. On cross-sectional echocardiography, the mass was 55 g (range 12 to 126) or 64 g/m^2 (range 46 to 79); on MRI it was 60 g (range 33 to 87) or 69 g/m^2 (range 46 to 89). Regression analysis yielded an r value of 0.98 with a standard error of the estimate of 5.7 g or a 10% difference. In older children, LV mass determined by MRI was bigger than the one derived by echocardiography. It is concluded that cross-sectional echocardiography can reliably assess LV myocardial mass in pediatric patients.

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Left ventricular (LV) mass may be important in the follow-up of patients with left-sided cardiac obstruction[1] and may play a role in epidemiologic studies of childhood hypertension.[2] Surgical decision regarding timing of surgery in complete transposition of the great arteries[3,4] or tricuspid atresia[5] may be influenced by LV myocardial mass. We had previously published normal values of LV myocardial mass in 95 control subjects with normal hearts ranging from newborns to adolescents.[6] To further validate the echocardiographically determined data, we examined 14 children by cross-sectional echocardiography and the nuclear magnetic resonance imaging (MRI) technique.

METHODS

Patients: The patients either had a structurally normal heart (n = 7) or had undergone repair of an aortic coarctation (n = 7) 2 to 3 years before the study. All of the latter group had arm systolic blood pressure within the 95th percentile[7] and none had a systolic pressure gradient between ascending and descending aorta of >20 mm Hg determined by Doppler echocardiography. The echocardiographic study had been performed in all patients on the same day as the MRI study.

Echocardiography: Commercially available equipment consisting of an Ultramark 9 sector scanner by Advanced Technology Laboratories or a Hewlett-Packard 1000 sector scanner was used for the echocardiograms, which were obtained with either a 5 or 7.5 mHz transducer. The images were recorded on ½-inch videocasette tape. For all children the standard apical 4- and 2-chamber views were used for analysis of LV mass. Using an offline computer (Kontron 200) the epicardium and subsequently the endocardium were manually traced on the electronic drawing board with a light pen in the 2 imaging planes. The entire ventricular septum was considered to be part of the left ventricle. The epicardial and endocardial volumes were calculated by dividing the LV shape into slices of 2 mm and adding up the single slice volumes applying the geometric formula of Simpson.[8] After the biplane epicardial and endocardial volumes had been measured, LV mass was calculated from the difference between epicardial and endocardial LV volume times the specific gravity of the heart (1.050).[9] LV mass volume index[10] was calculated as LV

TABLE I Clinical Data and Data on Left Ventricular Mass Determined by MRI or Echocardiography

Pt.	Age (yr) & Sex	Heart Disease	Mass by MRI (g)	Mass by Echo. (g)
1	10 days M	0	12.6	11.5
2	0.8 F	0	21.6	20.6
3	1.0 M	0	30.5	26.8
4	6.0 F	0	38.5	38.5
5	6.6 M	0	46.2	52.0
6	8.1 M	0	95.0	82.4
7	14.7 M	0	142.8	126.4
8	1.6 M	C of A	36.0	32.3
9	2.2 M	C of A	35.8	42.3
10	2.3 M	C of A	35.5	33.3
11	3.3 M	C of A	48.0	35.0
12	6.4 F	C of A	55.6	54.6
13	8.9 M	C of A	89.8	80.2
14	10.9 M	C of A	115.5	98.0

C of A = coarctation of the aorta; Echo. = echocardiography; MRI = magnetic resonance imaging; 0 = none.

muscle mass at end-diastole divided by LV end-diastolic volume. For the measurement of LV endocardial and epicardial volumes, 3 consecutive systolic and diastolic echocardiographic frames were analyzed and the mean of these 3 measurements calculated.

Magnetic resonance imaging technique: MRI was performed by use of a Philips Gyroscan S 15 with a 1.5 Tesla magnet. Uncooperative patients were sedated with chloralhydrate, 70 to 80 mg/kg body weight. Children weighing <18 kg were examined in the so-called head coil, which has a 32 cm (12.8 inches) diameter; children weighing >18 kg were examined in the so-called body coil, which has a 50 cm (20 inches) diameter. Imaging was triggered to the patients electrocardiogram, and a double echo technique with echo times of 30 and 60 ms was used. Acquisition and reconstruction matrix had 256 × 256 pixels. To shorten study time, a multisclice technique was used. Thus, images were obtained at multiple points in the cardiac cycle. The slice thickness was 3 to 5 mm. T1 weighted images were acquired in 3 orthogonal planes. In the axial tomograms the myocardial cross-sectional area (A) was assessed in n = k slices and multiplied with slice thickness (th). Myocardial volume (mV) was calculated as:

$$mV = \sum_{n=1}^{k} \text{Sum} \times A \times th$$

Myocardial mass was obtained by multiplying myocardial volume by 1.05.[9]

Statistical analysis: Data are given as mean ± standard deviation. Linear regression analysis was used to determine correlation between LV mass assessed by different imaging modes. For comparison of data a paired students *t* test was performed. A p value <0.05 was considered to indicate a significant change.

RESULTS

The results of the echocardiographic and MRI measurements of LV mass are listed in Table I for each individual child. With cross-sectional echocardiography the mass was 55 g (range 12 to 126) or 64 g/m^2 (range 46 to 79), and with MRI it was 60 g (range 33 to 87) or 69 g/m^2 (range 46 to 89). Figure 1 shows the correlation curve between echocardiographic and MRI mass assessment. The standard error of estimate was 5.7 g or 10%.

DISCUSSION

Noninvasive assessment of left ventricular mass: Several clinical or epidemiologic studies have used serial LV myocardial mass measurements.[2,11,12] A repeatable, noninvasive method of LV mass determination thus seems desirable. The surface electrocardiogram, although highly specific, lacks sensitivity.[13] Noninvasive imaging modes for assessing LV mass include, among others,[14,15] M-mode[16] or cross-sectional echocardiography[6] and MRI.[17-19] We did not examine accuracy of

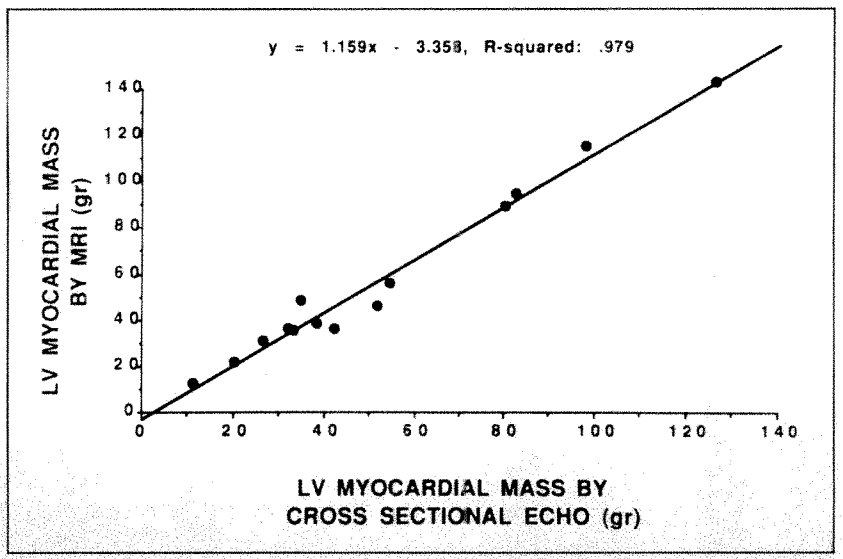


FIGURE 1. Correlation curve between echocardiographic (ECHO) and magnetic resonance imaging (MRI) left ventricular (LV) mass assessment.

M-mode determination of LV mass in this study. Data from published reports comparing LV mass at autopsy with M-mode echocardiographically determined mass have shown a variable correlation.[16,20,21] In a previous study in normal children, we found a good reproducibility of cross-sectional echocardiographic LV mass determinations[6] when assessing interobserver variability of measuring LV mass offline from a videotape. So far, all echocardiographic studies have been performed by one person (MV), but we appreciate that variability of cross-sectional echocardiographic mass determination may be substantially higher if image acquisition is performed by different observers. Cross-sectional imaging of the heart may be difficult in obese and adolescent patients, and accurate LV mass determination by cross-sectional echocardiography may not be possible.[22] MRI may become the golden standard of LV mass determination because there is usually little difficulty in defining endo- and epicardial borders (if errors by blood flow signals are excluded by appropriate techniques as double-echo or presaturation techniques). Usually there is no difficulty in imaging the cardiac apex, and obesity of a patient does not interfere with image quality in MRI. Another advantage of MRI may be that mass determination is not influenced by the geometric complexity of the heart.[18] The echocardiographic study used a Simpsons rule algorithm to calculate epi- and endocardial volume. Simpsons rule is based on the assumption of an elliptical shape, the minor and major axis of which are defined by 2 rectangular projections. The above-mentioned formula used to calculate volumes in the MRI study is independent of the real shape, since the area of each tomographic slice is manually outlined. Further studies with diseased hearts will show whether this theoretical advantage has practical implications for the accuracy of mass determination with MRI versus echocardiography.

Validation of magnetic resonance imaging method: The accuracy of the MRI technique had been assessed in an experimental study using 20 water-filled balloons of different irregular shapes containing volumes ranging from 50 to 300 ml. The correlation between measured volume and MRI-estimated volume was 0.99 (SEE 2.7%).[23] Although to date we have no autopsy data on any of our children, whose mass had been determined by MRI or cross-sectional echocardiography, these data are available in published reports and have shown good correlation between MRI-estimated mass and the true heart weight from human cadavers.[18]

Limitations of magnetic resonance imaging: In most in vivo MRI studies there was an overestimation of ventricular mass.[17-19] In our clinical study MRI mass was usually higher than mass determinded by cross-sectional echocardiography. This possible overestimation of myocardial mass by MRI may be related to partial volume effects and the presence of intracavitary flow signals.[18,19,24]

MRI studies in most pediatric patients aged <6 years and in some older children require sedation, and anxiety has been well documented in patients undergoing MRI studies.[25] Imaging time was longer than that used for echocardiographic assessment of the heart.

A multislice technique, which was used because of time constraints in our study, does not allow for comparison of end-systolic and end-diastolic mass (which is another valid method of studies determining mass) because the cardiac mass does not change during the cardiac cycle.[10] Accuracy of LV mass measurement by MRI can be improved by use of multicycled double angulated scans. With this technique slices perpendicular to the main axis of the left ventricle and triggered at the same time as the cardiac cycle are used. We had previously shown that the mean error between the multislice technique used in this study and the multicycled scans is 13%. However, the latter method has the disadvantage of a significantly longer imaging time.

Correlation of echocardiography and magnetic resonance imaging: The correlation between both methods of LV mass determination has been satisfactory. From our relatively small proband number we get the impression that this correlation is better in infants and smaller children than in adolescents. The applicability of cross-sectional echocardiographic mass measurements may be limited to newborns, infants and younger children. Further studies need to be done to define more exactly the influence of age and body composition on the accuracy of cross-sectional echocardiographic mass determination.

Acknowledgment: We thank Helen von Bibra, MD, for letting us use her Hewlett-Packard sector scanner for part of the study.

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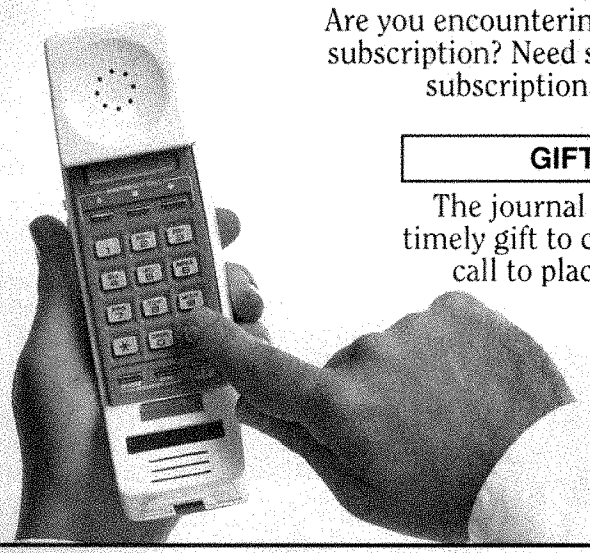
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Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients: Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Beta-Blocking Agents:*** A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism*.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28* times the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy: ***Pregnancy Category C:*** *Teratogenic Effects*. Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers: It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine, MSD) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (Incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL % N = 730		Placebo % N = 283
Peripheral Edema	22.3	(4.2)	3.5
Headache	18.6	(2.1)	10.6
Flushing	6.4	(1.0)	1.1
Dizziness	5.8	(0.8)	3.2
Upper Respiratory Infection	5.5	(0.1)	1.1
Asthenia	4.7	(0.1)	2.8
Cough	2.9	(0.0)	0.4
Paresthesia	2.5	(0.1)	1.8
Dyspepsia	2.3	(0.0)	1.4
Chest Pain	2.1	(0.1)	1.4
Nausea	1.9	(0.8)	1.1
Muscle Cramps	1.9	(0.0)	1.1
Palpitation	1.8	(0.5)	2.5
Abdominal Pain	1.8	(0.3)	1.1
Constipation	1.6	(0.1)	1.1
Diarrhea	1.6	(0.1)	1.1
Pharyngitis	1.6	(0.0)	0.4
Rhinorrhea	1.6	(0.0)	0.0
Back Pain	1.6	(0.0)	1.1
Rash	1.5	(0.1)	1.1

*Based on patient weight of 50 kg.

In the two dose response studies using PLENDIL® (Felodipine, MSD) as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related:

Adverse Effect	Placebo N = 121	5.0 mg N = 72	10.0 mg N = 123	20 mg N = 50
Peripheral Edema	2.5	13.9	19.5	36.0
Palpitation	0.8	0.0	2.4	12.0
Headache	12.4	11.1	18.7	28.0
Flushing	0.0	2.8	8.1	20.0

In addition, adverse experiences that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical studies (listed in order of decreasing severity within each category) and serious adverse events that occurred at a lower rate or were found during marketing experience (those lower rate events are in italics) were: *Body as a Whole:* Facial edema, warm sensation; *Cardiovascular:* Tachycardia, *myocardial infarction, hypotension, syncope, angina pectoris*, arrhythmia; *Digestive:* Vomiting, dry mouth, flatulence; *Hematologic:* *Anemia*; *Musculoskeletal:* Arthralgia, arm pain, knee pain, leg pain, foot pain, hip pain, myalgia; *Nervous/Psychiatric:* Depression, anxiety disorders, insomnia, irritability, nervousness, somnolence; *Respiratory:* Bronchitis, influenza, sinusitis, dyspnea, epistaxis, respiratory infection, sneezing; *Skin:* Contusion, erythema, urticaria; *Urogenital:* Decreased libido, impotence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also been studied as monotherapy in 680 patients with hypertension in U.S. and overseas controlled clinical studies. Other adverse experiences not listed above and with an incidence of 0.5 percent or greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointestinal pain; *Musculoskeletal:* Arthritis, local weakness, neck pain, shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respiratory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurred vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in < 0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients*.)

Clinical Laboratory Test Findings: ***Serum Electrolytes:*** No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, *Renal/Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE: Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended initial dose is 5 mg once a day. Therapy should be adjusted individually according to patient response, generally at intervals of not less than two weeks. The usual dosage range is 5-10 mg once daily. The maximum recommended daily dose is 20 mg once a day. That dose in clinical trials showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function, because they may develop higher plasma concentrations of felodipine, should have their blood pressure monitored closely during dosage adjustment (see PRECAUTIONS). In general, doses above 10 mg should not be considered in these patients.

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Short- and Midterm Results of Balloon Valvuloplasty for Valvular Aortic Stenosis in Children

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During a 27-month period, 21 consecutive children (aged 0.1 to 15.7 years) with isolated valvular aortic stenosis underwent percutaneous transfemoral balloon valvuloplasty. Ten children had undergone earlier surgical valvulotomy. The indication for treatment was ST-T-segment changes at rest or during bicycle-ergometry, a continuous-wave Doppler-derived transvalvular gradient >60 mm Hg or syncope, or a combination. Mean peak systolic left ventricular pressure decreased from 165 ± 19 to 131 ± 19 mm Hg ($p < 0.001$). Mean end-diastolic left ventricular pressure did not change significantly (12 ± 3 vs 11 ± 5 mm Hg). Mean peak systolic valve gradient decreased from 71 ± 23 to 22 ± 11 mm Hg ($p < 0.001$). Mean cardiac index remained unchanged (2.9 ± 0.8 vs. 3.0 ± 0.7 liters · min^{-1} · m^{-2}). Aortic valve regurgitation on angiography appeared or increased in 9 patients (up to grade 3 in 3 children). Noninvasive follow-up studies were performed for 2 to 4.2 years (mean 2.8). ST-T changes on the electrocardiogram at rest or during exercise were present in 6 patients before balloon valvuloplasty and had disappeared in all at 6-month follow-up. Reoccurrence of ST-T changes after a longer follow-up was associated with severe valve regurgitation. Syncope was not observed after balloon valvuloplasty. The continuous-wave Doppler gradient decreased from 94 ± 36 to 49 ± 15 mm Hg ($p < 0.001$). After a follow-up of 2 to 4.2 years (mean 2.8) it remained unchanged (43 ± 13 mm Hg; p = not significant). Aortic regurgitation on echocardiography appeared or increased initially in 11 patients. In some patients after longer follow-up, an additional increase was observed. At the latest follow-up, grade 3 aortic regurgitation was present in 5 patients, 3 of whom underwent valve replacement. These 3 patients had undergone earlier surgical valvulotomy. Except for age, weight and left ventricular end-diastolic pressure before valvuloplasty, there were no differences between the earlier operated and nonoperated patients. Aortic valvuloplasty is effective and postpones surgery in the majority of patients. Occurence or increase of aortic valve regurgitation may be induced, leading to valve replacement in 14% of patients within 2 years.

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The introduction of balloon valvuloplasty for valvular aortic stenosis in children prompted several investigators to use this technique as an alternative to surgical valvulotomy. Balloon valvuloplasty has been used as an initial treatment, as well as for restenosis after earlier surgical valvulotomy. Questions remain as to whether balloon valvuloplasty is the primary choice of treatment, because of the associated risks of this technique, such as the occurrence of valvular regurgitation.[1,2] In most studies data on follow-up are limited to 1 to 2 years.[3–7] In this study we describe our experience with balloon valvuloplasty for isolated valvular aortic stenosis in children (with 2 to 4.2 years of follow-up data), with special emphasis on the initial indications on the basis of which the balloon valvuloplasty was performed.

METHODS

Between April 1987 and July 1989, all children presenting consecutively at our institution with isolated valvular aortic stenosis and a continuous-wave Doppler-derived transvalvular gradient >60 mm Hg or ST-T-segment changes ≥2 mm on the electrocardiogram, at rest or during exercise, or both, were included in the study. Syncope was also an indication for treatment, even if the other criteria were not met. In patients with an invasive transvalvular pressure gradient <60 mm Hg, the aortic valve area had to be <0.7 $cm^2 \cdot m^{-2}$ to proceed to treatment. Patients with more than grade 2 valve regurgitation angiographically or with multiple cardiac malformations were not included. The inclusion criteria were fulfilled in 21 children. All 21 children (5 girls and 16 boys, mean age 7.7 years, range 0.1 to 15.9) had isolated valvular aortic stenosis, except one 5-year-old boy who underwent coarctation repair at the age of 1 day. Ten patients had undergone earlier surgical valvulotomy 2.1 to 11 years (mean 5.6) before balloon valvuloplasty. The continuous-wave Doppler pressure gradient was >60 mm Hg in 18 patients. Of these 18 patients, 1 had syncope, 2 had ST-T-segment changes at rest, and 2 had ST-T-segment changes at exercise. In the 3 patients with a Doppler pressure gradient <60

TABLE I Cardiac Catheterization Data Before and After Balloon Valvuloplasty for Valvular Aortic Stenosis

	Peak Syst. LV Press. (mm Hg)		End-Diast. LV Press. (mm Hg)		Peak Syst. Grad. (mm Hg)		Cardiac Index ($L \cdot min^{-1} \cdot m^{-2}$)		Aortic Valve Area ($cm^2 \cdot m^{-2}$)		Systemic Vascular Resist. ($U \cdot m^2$)	
Pt.	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1*	180	110	15	12	89	14	5.0[F]	3.3	0.53	0.89	14.2	20.9
2*	166	154	15	15	60	31	–	–	–	–	–	–
3	150	158	10	8	43	36	2.0	2.7	0.30	0.45	40.0	33.7
4	158	158	15	14	53	20	3.5	3.3	0.48	0.74	24.2	30.3
5	133	134	10	6	39	26	2.7	3.5	0.43	0.69	28.2	23.4
6	117	–	11	–	35	–	3.9	–	0.66	–	17.4	–
7*	136	140	12	12	43	12	2.3	2.4	0.35	0.69	30.4	46.2
8	183	147	14	10	69	11	2.7	3.3	0.32	1.00	26.3	28.8
9	185	113	12	11	118	24	2.3[F]	2.3	0.21	0.60	16.1	23.9
10*	178	126	10	8	78	29	3.1	2.5	0.35	0.46	19.7	22.4
11	172	106	8	7	91	27	4.2	4.0	0.44	0.87	14.8	15.0
12*	178	128	15	15	84	28	2.8	2.9	0.30	0.55	27.1	27.9
13*	158	143	13	25	66	36	2.7	2.4	0.30	0.44	26.7	34.6
14*	153	132	15	8	60	14	2.0	2.0	0.26	0.53	33.5	50.5
15	147	125	7	7	58	12	2.4	2.1	0.31	0.61	29.6	44.3
16	166	150	7	15	86	48	2.9	4.6	0.32	0.65	23.8	18.5
17*	152	145	14	8	39	21	3.0	2.3	0.48	0.50	30.0	44.4
18*	169	113	15	18	78	15	2.8	4.0	0.32	1.03	21.4	16.8
19*	187	124	14	10	98	14	2.5	3.2	0.25	0.81	28.4	26.9
20	201	127	9	8	113	12	2.3[F]	2.9	0.22	0.84	25.2	25.2
21	138	90	14	10	61	11	3.2[F]	3.0	0.41	1.13	19.1	21.7
	165 ± 19	131 ± 19	12 ± 3	11 ± 5	71 ± 23	22 ± 10	2.9 ± 0.8	3.0 ± 0.7	0.35 ± 0.09	0.71 ± 0.21	25.2 ± 6.6	29.2 ± 10.5
	$p < 0.001$		NS		$p < 0.001$		NS		$p < 0.001$		$p < 0.05$	

*Earlier surgical valvulotomy.
Diast. = diastolic; [F] = cardiac index by Fick method; Grad. = gradient; LV = left ventricular; NS = not significant; Press. = pressure; Resist. = resistance; Syst. = systolic.

mm Hg, 1 had syncope, and 2 had a positive exercise test. The indexed aortic valve area could be calculated in 19 patients (<0.7 $cm^2 \cdot m^{-2}$).

Noninvasive studies: Standard surface electrocardiograms were recorded. The presence of left ventricular hypertrophy on the electrocardiogram was assessed according to voltage criteria.[8] Bicycle ergometry was performed in patients with Doppler gradients <70 mm Hg. The electrocardiogram and exercise tests were judged positive when ST-T-segment changes ≥2 mm were present.

Echocardiography included M-mode and 2-dimensional studies combined with color-coded Doppler. Continuous-wave Doppler was used to determine pressure gradients. Aortic regurgitation was evaluated semiquantitatively by a combination of Doppler and 2-dimensional imaging. Absence of any leakage was judged as grade 0, a regurgitant jet not exceeding the level halfway to the anterior mitral valve leaflet as grade 1, and a jet reaching to a level between the middle and the tip of the anterior mitral valve leaflet as grade 2. If left ventricular dilatation was present in combination with a jet deep into the left ventricular cavity, and backflow in the aortic arch, the regurgitation was classified as grade 3. Electrocardiographic and echocardiographic studies were performed before and the day after valvuloplasty, after 6 and 12 months, and then yearly. Exercise studies at follow-up were performed in patients if the age was appropriate.

Invasive studies: Right- and left-sided heart catheterizations were performed under general anesthesia, including pressure measurements with fluid-filled catheters. Cardiac index was determined by means of the dye-dilution or Fick method. Aortic valve area was calculated with the simplified Gorlin and Gorlin formulas. A supravalvular aortogram was obtained to grade eventual aortic regurgitation on a scale of 0 of 4.[9] From the angiogram, annular diameter was measured. The balloon size chosen was 0.9 to 1 time that of the valve annulus. Only single balloons were used. From April 1989 in the older children, stiff guidewires were used to improve the stability of the balloon during inflation. Balloons were inflated 3 to 4 times, up to pressures of 3 to 4 atm. During the actual dilatation procedure, fractional inspired oxygen concentration was temporarily increased from 30 to 100%. After the procedure, pressures and cardiac index were measured again, and aortography was repeated. Bleeding from the groin after removal of the catheters was controlled by attentive local manual compression. Patients were observed for 6 to 18 hours after the procedure in the intensive care unit, with special regard to bleeding and diminished femoral artery perfusion.[10]

Data analysis: Group data are presented as mean ± SD, and range. Statistical analysis was performed using Student's paired or unpaired *t* test. Differences were considered significant at $p < 0.05$.

RESULTS

Cardiac catheterization data (Table I): Mean peak systolic left ventricular pressure was 165 ± 19 before and 131 ± 19 mm Hg after valvuloplasty ($p < 0.001$). Mean end-diastolic left ventricular pressure was 12 ± 3 mm Hg before and 11 ± 5 mm Hg after valvuloplasty (p = not significant [NS]). Mean peak systolic pressure difference between the left ventricle and aorta was 71 ±

23 mm Hg before and 22 ± 10 mm Hg after valvuloplasty ($p < 0.001$). In 19 patients, the cardiac index (15 dye, 4 Fick) was 2.9 ± 0.8 liters · min^{-1} · m^{-2} before and 3.0 ± 0.7 liters · min^{-1} · m^{-2} after valvuloplasty (p = NS). Mean aortic valve area index was 0.35 ± 0.09 $cm^2 \cdot m^{-2}$ before and 0.71 ± 0.21 $cm^2 \cdot m^{-2}$ after valvuloplasty ($p < 0.001$). Mean systemic vascular resistance index increased from 25.6 ± 6.6 to 29.2 ± 10.5 $U \cdot m^2$ ($p < 0.05$).

Angiographic data: Because severe femoral artery spasm after balloon valvuloplasty prevented repeat angiography in 1 five-month-old infant, 20 patients were studied. Aortography before balloon valvuloplasty revealed no regurgitation in 8 patients, grade 1 regurgitation in 5, and grade 2 in 7. After balloon valvuloplasty, the aortic valve was still competent in 2 patients. Regurgitation remained unchanged in 9 patients, increased 1 grade in 4, two grades in 3, and 3 grades in 2 (Figure 1). Of the 4 patients with grade 3 regurgitation after balloon valvuloplasty, 2 did not have regurgitation before valvuloplasty, 1 had grade 1 regurgitation, and 1 had grade 2.

Electrocardiographic and exercise studies: Before balloon valvuloplasty, electrocardiography showed left ventricular hypertrophy without ST-T changes in 16 patients, 10 of whom had no left ventricular hypertrophy 6 months after balloon valvuloplasty. In 3 patients, the electrocardiogram before valvuloplasty was normal, but showed left ventricular hypertrophy in 2 of them at 6-month follow-up. Before balloon valvuloplasty, electrocardiography at rest showed ST-T changes with signs of left ventricular hypertrophy in 2 patients; 6 months after balloon valvuloplasty, the ST-T changes had disappeared in both patients. In 1 of these patients, who had severe aortic regurgitation after balloon valvuloplasty, ST-T changes reappeared after 2 years. In 1 patient with left ventricular hypertrophy before balloon valvuloplasty, left bundle branch block occurred during balloon valvuloplasty and persisted up to 6 months, but had disappeared at 12 months. Exercise studies were performed in 4 patients before balloon valvuloplasty and were abnormal with respect to ST-T-segment changes. The exercise-induced ST-T changes had disappeared in all 4 patients 6 months after balloon valvuloplasty. Another patient with severe regurgitation after balloon valvuloplasty had short runs of ventricular tachycardia at 12 months, although there were no abnormalities at exercise at 6-month follow-up.

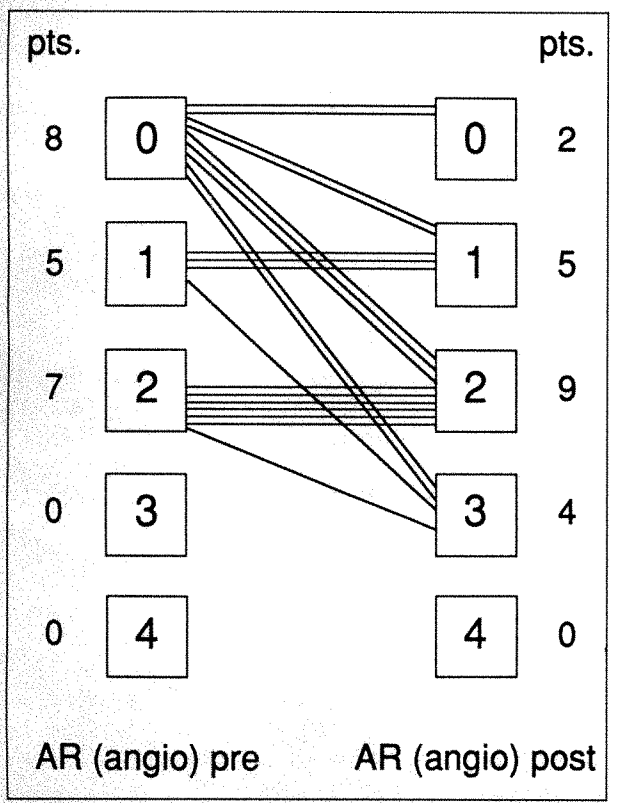


FIGURE 1. Angiographically (angio) determined aortic valve regurgitation (AR) before and after valvuloplasty.

Doppler echocardiography: The transvalvular pressure gradient determined with continuous-wave Doppler decreased from 94 ± 36 to 49 ± 15 mm Hg the day after balloon valvuloplasty ($p < 0.001$). At 6-month follow-up, the pressure gradient was 48 ± 15 mm Hg (p = NS), and at 12 months, 45 ± 13 mm Hg (p = NS). At the latest follow-up (range 2 to 4.2 years, mean 2.8), the Doppler gradient was 43 ± 13 mm Hg (p = NS; Figure 2). Aortic valve competence 1 day after balloon valvuloplasty was still present in 3 patients. Regurgitation remained unchanged in 7 patients, and increased 1 grade in 8, two grades in 1, and 3 grades in 2. During follow-up, changes also were observed (Figure 3). In 4 patients, grade 1 regurgitation increased to grade 2, and in 3, grade 2 increased to grade 3. At the latest follow-up, 5 patients were judged to have grade 3 aortic regurgitation, 3 of whom underwent valve replacement.

Short-term complications: There were no deaths. Substantial bleeding from the groin occurred in 5 patients needing transfusion. Femoral artery thrombosis occurred in 4 patients (19%), 3 of whom were aged <5 months. All 4 patients were treated with streptokinase with good results, except 1 who initially persisted to have impaired pedal pulses. However, at follow-up, pulsations of both legs were equal. The increase of aortic regurgitation from grade 0 to 3 in 2 patients did not

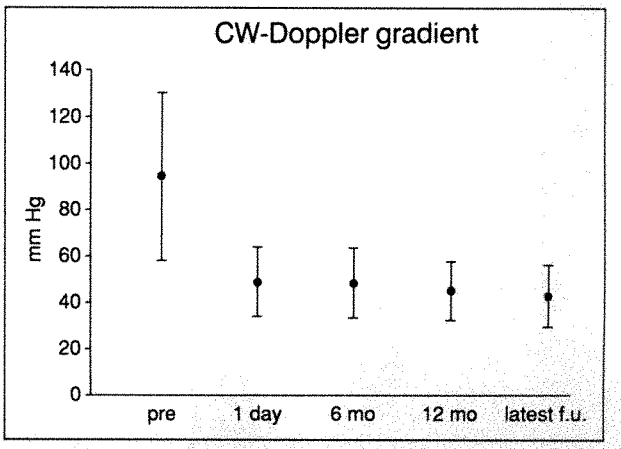


FIGURE 2. Transvalvular aortic gradient determined with continuous-wave (CW) Doppler before valvuloplasty, at 1 day, 6 and 12 months, and at latest follow-up (f.u.).

TABLE II Comparison of Children Who Did or Did Not Undergo Earlier Surgical Valvotomy

	Surgery (n = 10)	No Surgery (n = 11)	p Value
Age (yr)	10.6 ± 3.8	5.1 ± 4.2	<0.01
Weight (kg)	34 ± 12	19 ± 11	<0.01
Peak syst. LV press. (pre) (mm Hg)	166 ± 16	160 ± 25	NS
Peak syst. LV press. (post) (mm Hg)	132 ± 14	131 ± 23	NS
End-diast. LV press. (pre) (mm Hg)	14 ± 2	11 ± 3	<0.01
End-diast. LV press. (post) (mm Hg)	13 ± 5	10 ± 3	NS
Peak syst. gradient (pre) (mm Hg)	70 ± 20	70 ± 29	NS
Peak syst. gradient (post) (mm Hg)	21 ± 9	23 ± 12	NS
Aortic valve area (pre) ($cm^2 \cdot m^{-2}$)	3.35 ± 0.11	0.37 ± 0.12	NS
Aortic valve area (post) ($cm^2 \cdot m^{-2}$)	0.64 ± 0.20	0.79 ± 0.18	NS
Cardiac index (pre) ($L \cdot min^{-1} \cdot m^{-2}$)	2.9 ± 0.8	2.9 ± 0.7	NS
Cardiac index (post) ($L \cdot min^{-1} \cdot m^{-2}$)	2.8 ± 0.6	3.2 ± 0.8	NS
Systemic vasc. resist. (pre) ($U \cdot m^2$)	25.7 ± 6.1	24.1 ± 7.3	NS
Systemic vasc. resist. (post) ($U \cdot m^2$)	32.2 ± 12.2	26.5 ± 8.4	NS
CW Doppler gradient (pre) (mm Hg)	92 ± 34	97 ± 39	NS
CW Doppler gradient (post) (mm Hg)	47 ± 18	50 ± 12	NS
CW Doppler gradient (6 mos) (mm Hg)	48 ± 21	49 ± 9	NS
CW Doppler gradient (12 mos) (mm Hg)	45 ± 15	45 ± 10	NS
CW Doppler gradient (latest) (mm Hg)	42 ± 17	43 ± 10	NS

CW = continuous-wave; vasc. = vascular; other abbreviations as in Table I.

lead to acute clinical problems, and both were discharged 2 days after balloon valvuloplasty. In 1 patient, a left bundle branch block pattern on the electrocardiogram was still prominent on the day of discharge.

Clinical follow-up: Syncope did not occur in any patient after balloon valvuloplasty. Clinical condition was good, even in patients who developed substantial aortic regurgitation acutely or later. Aortic valve replacement was performed in 3 patients between 1 and 2 years after valvuloplasty. All 3 patients had undergone surgical valvulotomy before balloon valvuloplasty. The indication for valve replacement was severe aortic regurgitation and short runs of ventricular tachycardia during exercise in 1 patient (Table I, patient 13), and echocardiographically, a grade 3 aortic regurgitation leading to progressive left ventricular dilatation in the 2 other patients (Table I, patients 10 and 19). In these patients, the aortic root was successfully replaced by a pulmonary autograft, and an allograft was placed in the pulmonary position.[11] The other 2 children with substantial regurgitation are followed at half-year intervals.

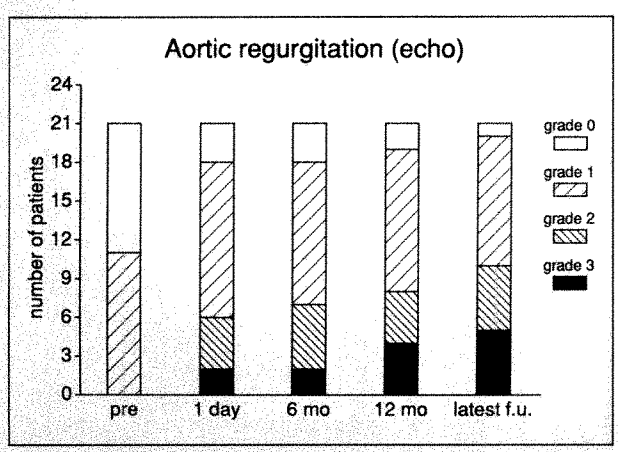


FIGURE 3. Aortic valve regurgitation determined with Doppler echocardiography (echo) before valvuloplasty, at 1 day, 6 and 12 months, and at latest follow-up (f.u.).

Outcome related to eventual earlier surgery: A comparison was performed between patients who had undergone earlier surgical valvotomy and those with no previous no treatment (Table II). Age and weight were significantly greater in patients who had undergone earlier surgery. Invasively determined hemodynamic parameters were not different between both groups, except for end-diastolic left ventricular pressure before balloon valvuloplasty, which was slightly lower in the nonoperated group. Doppler-derived pressure gradients were not

significantly different between both groups before or after valvuloplasty. The increase in regurgitation angiographically was not significantly different between both groups. Echocardiographically, there was no difference between the groups, nor shortly after valvuloplasty, nor at follow-up. However, the need for valve replacement only occurred in the operated group.

DISCUSSION

The treatment of aortic valve stenosis in children aims to preserve left ventricular function and to prevent acute and chronic complications.[12] To assess the severity of the stenosis, the transvalvular pressure gradient is a practical measurement, especially when obtained with continuous-wave Doppler. Compared with invasively measured gradients, continuous-wave Doppler tends to overestimate the gradient owing to the difference in peak-to-peak versus a peak instantaneous measurement. In contrast, invasively measured transvalvular pressure gradients obtained under general anesthesia may underestimate the severity of the stenosis owing to factors such as diminished cardiac output. Therefore, cardiac output should be taken into account, and aortic valve area calculated. Furthermore, one should realize that in some patients the ventricular response (i.e., functional severity of stenosis) may not be reflected by the transvalvular gradient and aortic valve area. Changes of the ST-T-segment interpreted as a sign of subendocardial ischemia and syncopal attacks may occur in patients with only moderate transvalvular gradients. Because this has been associated with morbidity and mortality, patients with such a presentation were also judged to have an indication for treatment.[12] In this study, balloon valvuloplasty directly resulted in a 20% reduction of peak systolic left ventricular pressure, and a 64% decrease in the transvalvular gradient. The only moderate reduction of peak systolic left ventricular pressure without changes in cardiac index must be explained by a concomitant increase in systemic vascular resistance, of which the cause is unclear. Several factors may explain this feature. The vasoconstrictive effect of an elevated inspired oxygen concentration may still be present at the time of sampling. In addition, probably due to the effect of general anesthesia, the absolute systolic pressures are relatively low, so the effect on left ventricular systolic pressure (as measured invasively) is only limited. The follow-up data only relate to noninvasive studies. This in part limits evaluation of the safety and efficacy of the use of balloon valvuloplasty as an alternative for surgical valvotomy. The gradient reduction (as measured with continuous-wave Doppler) was not as large as that measured invasively (48 vs 64%). Restenosis at follow-up was not observed. Furthermore, in the presence of significant regurgitation, the continuous-wave Doppler gradient overestimates the gradient. Occurrence or increase of aortic regurgitation was noted in 45% of patients after balloon valvuloplasty. Although during follow-up in some patients an increase in aortic regurgitation occurred, none needed surgical intervention. The 3 patients that did need valve replacement within 1 to 2 years had grade 3 aortic regurgitation on angiography directly after balloon valvuloplasty, and 1 had a markedly elevated end-diastolic left ventricular pressure. The acute increase in aortic regurgitation was also reported by other investigators.[1-5] The reasons for this increase are both technical and morphologic. Hazardous movements of the balloon may be prevented by using longer balloons in combination with a stiff guidewire, especially in older children. However, in patients that underwent balloon valvuloplasty after July 1989 (not included in this study) using such a guidewire, substantial progression of aortic regurgitation was still observed. Measurements of the valve annulus were obtained from the aortogram, which are (in our experience) comparable to those from the left ventriculogram. The measurements were obtained from the videoscreen with a calibration grid, but even the use of a grid does not warrant a completely reliable measurement: There was no relation between the relative size of the balloon used and the occurence or progression of valve regurgitation. Transesophageal echocardiography can elucidate the valve morphology, and the positioning of the balloon and guidewire.[13] However, it remains questionable if a better knowledge of the valve morphology will provide more insight to the potential risk of inducing aortic valve regurgitation by balloon valvuloplasty. Our results confirm the findings of a recent study that a further increase in regurgitation is observed during follow-up in some patients.[1] Prolapse of the aortic valve, associated with rupture of the valve cusp due to valvuloplasty, is suggested to be progressive, especially when commissural support is absent. In our patients with progressive regurgitation we have not been able to document any prolapse (neither at echocardiographic examination or at surgery for valve replacement). Except for age, weight and left ventricular end-diastolic pressure before valvuloplasty, there were no differences between the earlier operated and nonoperated patients. However, the need for valve replacement occurred only in patients who had undergone earlier surgical valvulotomy. Regarding the indication for treatment, the continuous-wave Doppler gradient decreased to <60 mm Hg in all except 3 patients. Two of these patients also had substantial regurgitation that was likely to overestimate the gradient with continuous-wave Doppler. In the third patient, the valve gradient after balloon valvuloplasty was slightly >60 mm Hg and remained unchanged during 2-year follow-up. However, before treatment, this patient had ST-T-changes during exercise, which disappeared after balloon valvuloplasty and did not reoccur at follow-up. Furthermore, all other patients with ST-T changes at rest or during exercise had normal ST-T segments shortly after balloon valvuloplasty. Reoccurrence of these changes was clearly associated with the presence of severe aortic regurgitation with ventricular dilatation. Syncopal attacks did not occur in the few patients who presented with this complaint before balloon valvuloplasty. This study confirms the usefulness of exercise studies in these patients also after earlier surgical valvulotomy.[14] In summary, 17 of 21 patients in this study definitely benefited from balloon valvuloplasty with regard to the initial indication for treatment. In 4 patients, the result was questionable owing to either the occurrence of severe aortic regurgitation or persistence

of a substantial gradient. The immediate complications are acceptable, although femoral artery thrombosis (especially in children aged <1 year) can prolong hospital stay and costs. Longer term follow-up data are needed for a more definite evaluation of balloon valvuloplasty for valvular aortic stenosis in children.

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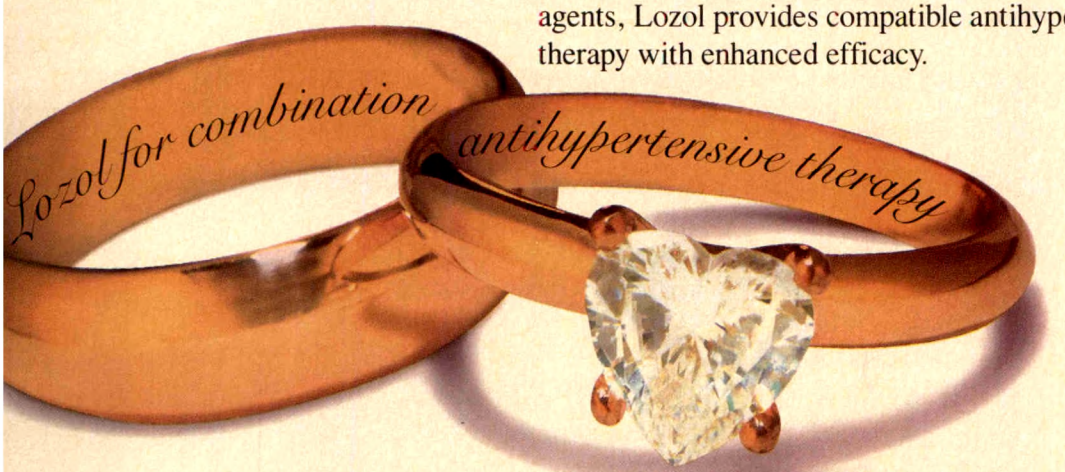
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INDAPAMIDE 2.5mg

Please see brief summary of prescribing information below.

LOZOL® (indapamide) **2.5 mg tablets**
BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (see ADVERSE REACTIONS, hypokalemia), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; < 5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloramia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Clinical hypokalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study (157 patients) potassium supplementation was given to 12% and 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at room temperature. Avoid excessive heat.
Dispense in tight containers as defined in USP.
See product circular for full prescribing information. Revised: June 1990

References: 1. IMS National Prescription Audit (NPA). August 1991. Compared with year-to-date August 1991 percentage growth in new prescriptions among the 10 leading brands of diuretics. 2. Scott-Levin Physician Drug and Diagnosis Audit (PDDA). July 1990–June 1991.

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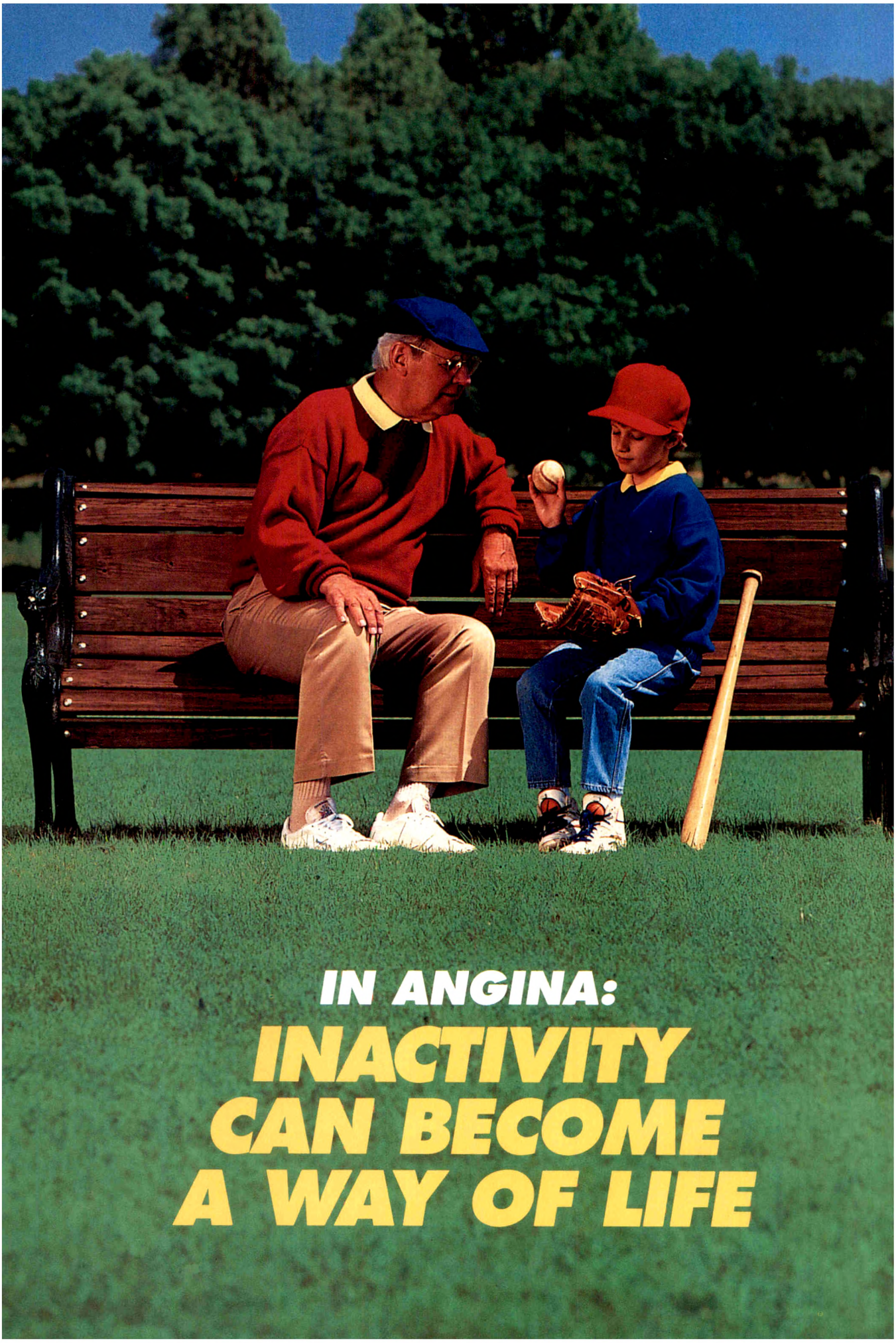
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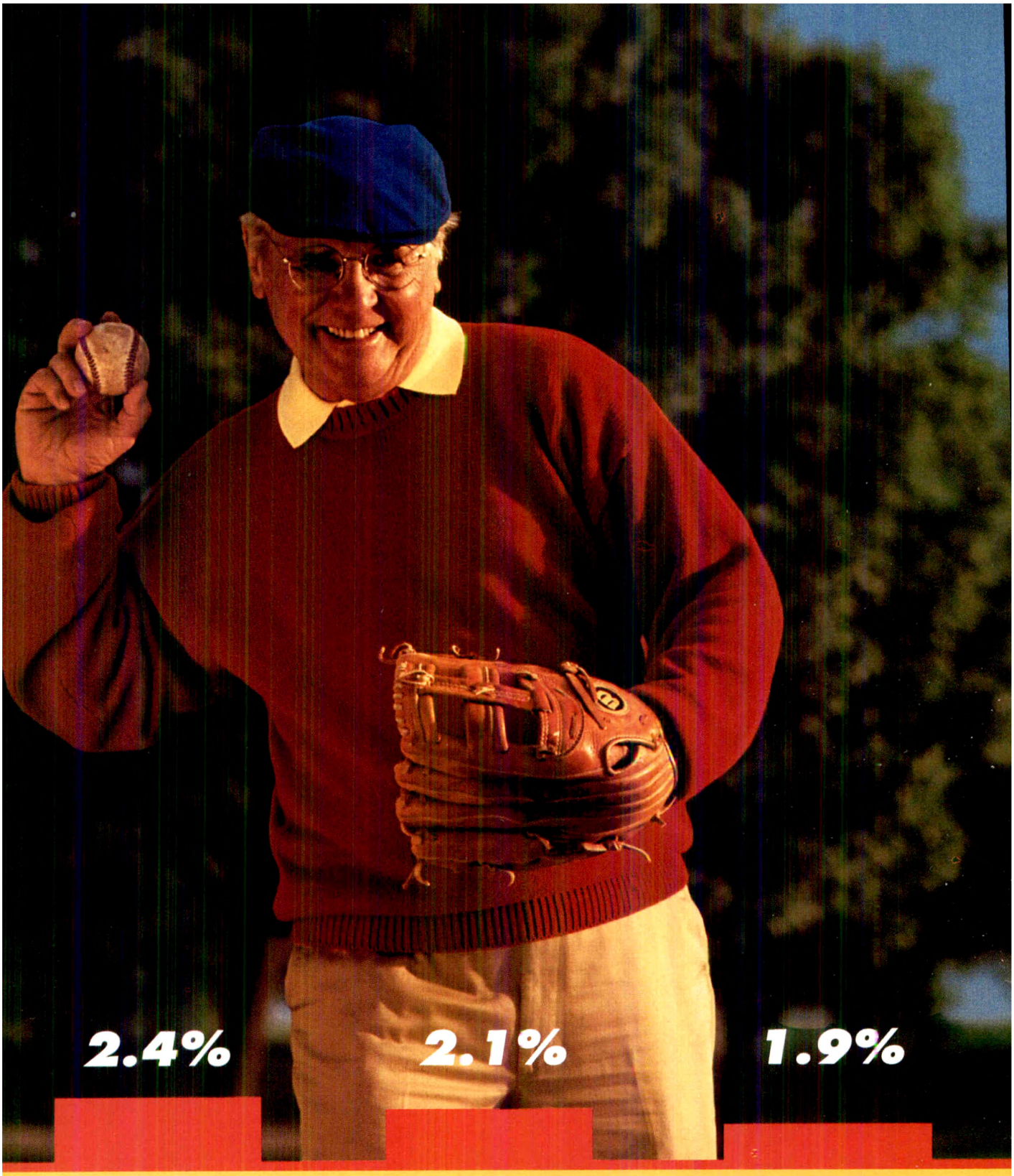
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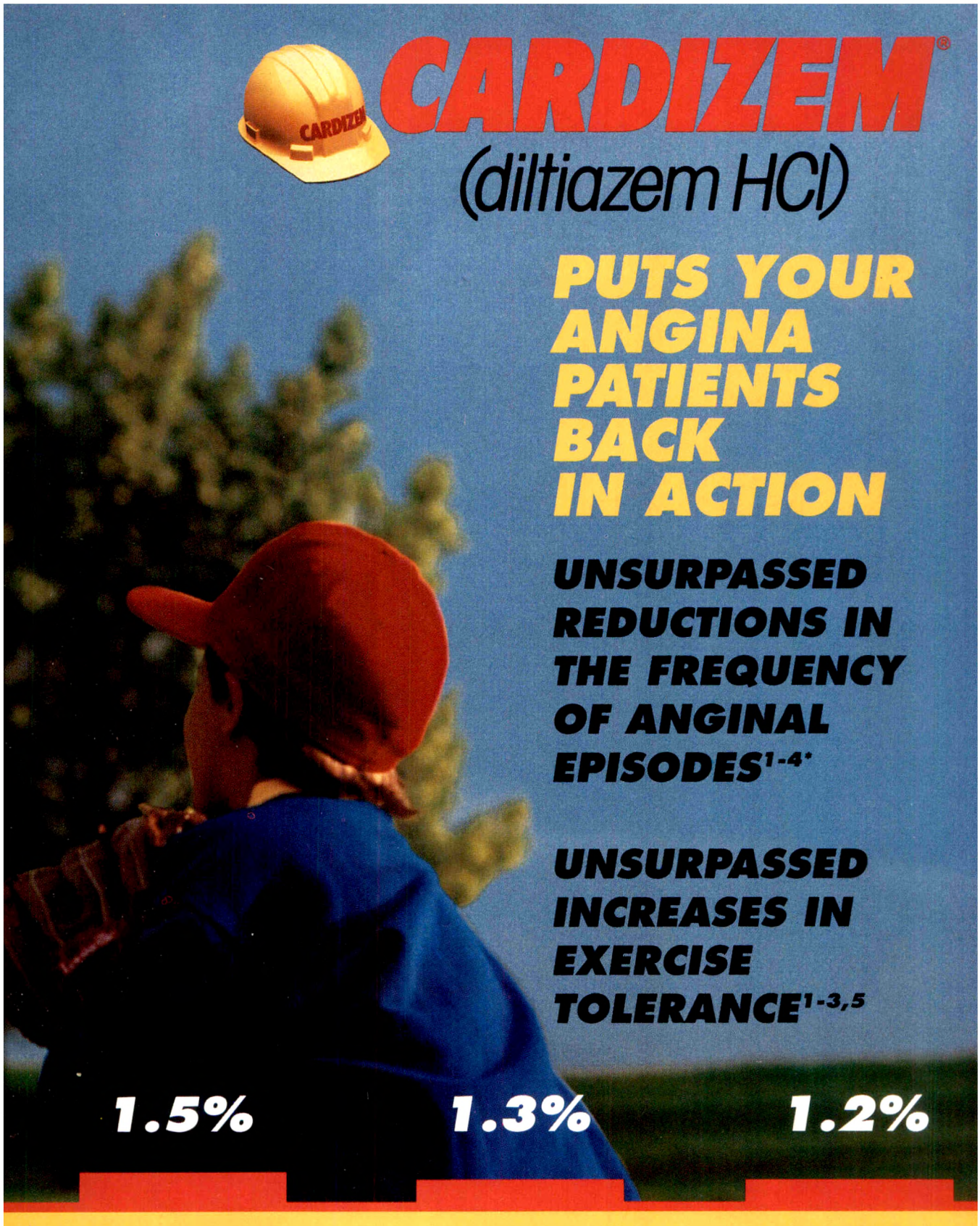


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* CARDIZEM ® (diltiazem HCl) is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic despite adequate doses of these agents.

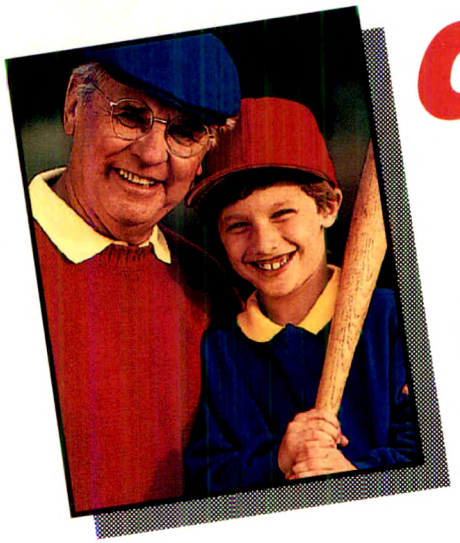
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ngina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic

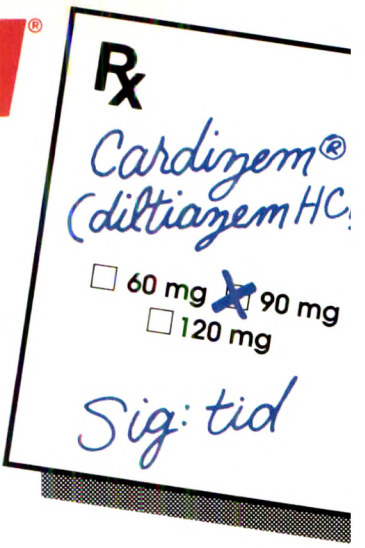
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Please see brief summary of prescribing information on next page.



CARDIZEM®
(diltiazem HCl)

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BRIEF SUMMARY

CARDIZEM®
(diltiazem hydrochloride)
Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences from these studies, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

Issued 1/91

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Circadian Variation in Platelet Function in Healthy Volunteers

Syed M. Jafri, MD, Mike VanRollins, PhD, Tsunenori Ozawa, MD, Eberhard F. Mammen, MD, A. David Goldberg, MD, and Sidney Goldstein, MD

Circadian variation in hemostatic factors may contribute to a higher frequency of cardiac events observed in the morning and with activity. Diurnal changes in these factors were investigated by measuring in vitro platelet aggregability in response to epinephrine and adenosine diphosphate together with β-thromboglobulin and platelet factor 4 as indexes of in vivo platelet activation. Activation of coagulation was measured by thrombin–antithrombin III complexes and D-Dimers. Tests were performed in 9 normal healthy subjects. Circadian changes occurred in β-thromboglobulin ($p < 0.05$) and platelet factor 4 ($p < 0.06$). Plasma levels of β-thromboglobulin and platelet factor 4 were lowest with patients supine and resting at 7 and 8 A.M., and increased with activity, with peak levels achieved at 3 P.M. ($p < 0.01$). Thrombin–antithrombin III complexes ($p = 0.44$), D-Dimer ($p = 0.36$) and in vitro platelet aggregability to adenosine diphosphate ($p = 0.20$) did not show diurnal variation. There was a trend toward circadian variation in vitro platelet aggregability to epinephrine, but these changes did not achieve statistical significance ($p = 0.16$). Circadian changes of in vivo release of β-thromboglobulin and platelet factor 4 correlated to patient activity and not to the morning peaks in ischemic events. These data indicate that changes in platelet function and not in coagulation have a diurnal occurrence.

(Am J Cardiol 1992;69:951–954)

From the Heart and Vascular Institute, Henry Ford Hospital, and Wayne State University School of Medicine, Detroit, Michigan. Manuscript received September 16, 1991; revised manuscript received December 6, 1991, and accepted December 7.

Address for reprints: Syed M. Jafri, MD, Heart and Vascular Institute K-14, Henry Ford Hospital, 2799 W. Grand Blvd., Detroit, Michigan 48202.

Circadian variation of factors that increase the risk of thrombus initiation or decrease the rate of thrombus removal can be an important trigger mechanism for coronary thrombosis. Platelet activation and antifibrinolytic tendency have been shown to follow a diurnal rhythm and possibly relate to the peak time of onset of myocardial infarction and sudden death.[1,2] Platelet responses to activation include adhesion, aggregation and secretion. Platelet aggregability is determined by evaluating in vitro responses to platelet aggregating agents.[3,4] Increased plasma levels of platelet release proteins β-thromboglobulin and platelet factor 4 reflect platelet release reaction and are considered an index of in vivo platelet activation.[5,6] This study was performed to investigate the relation of diurnal changes in in vitro platelet aggregation[1,2] to the simultaneous in vivo release of platelet release proteins. Furthermore, we investigated the diurnal changes in markers of activation of coagulation, thrombin-antithrombin III complexes and D-Dimers.[7,8]

METHODS

Study group: The study group comprised 9 healthy subjects (4 men and 5 women, mean age 51 ± 10 years) who had no known disease and had not received any medication within the preceding 2 weeks before the study. The protocol was approved by the human rights committee, and written informed consent was obtained from all patients.

Study protocol: Patients were admitted to a private room, and venipunctures were performed with the patient in a seated position at 3, 6 and 9 P.M. on day 1 of the study. Patients were ambulatory until 10 P.M., and slept at 11 P.M. On day 2, blood samples were obtained with the patient resting and in a supine position at 7 and 8 A.M. Between 9 and 10 A.M. they walked down the hallways, climbed stairs and used a stationary exercise bicycle, and remained active for the remainder of the day. Blood samples were obtained in a seated position at 10 A.M., 12 noon and 3 P.M.

Blood sample collection: Precautions were taken to minimize the potential for activation of platelets and clotting during blood sampling. A separate venipuncture was performed at each time point. An initial 3 ml blood sample was discarded. The next 27 ml of blood were collected in a plastic syringe containing 3 ml of 1.24 M sodium citrate and 1.36 M glucose (pH 6.5) for platelet aggregation studies. The next 9 ml of blood were collected in a plastic tube containing sodium citrate, theophylline, adenosine and dipyridamole (Diatube-H, American Bioproducts, Parsippany, New Jersey), and placed on crushed ice. The next 9 ml of blood were col-

lected in a plastic tube containing 1 mg of 2.8% sodium citrate solution, and also placed in ice. These blood specimens were centrifuged at 4°C at 2,000 g for 30 minutes, and plasma samples were frozen at −70°C for batch analysis. The upper third of the plasma was separated from the first tube for analysis of platelet factor 4 and β-thromboglobulin. D-Dimer and thrombin–antithrombin III complexes were assayed using the citrated plasma.

Platelet aggregation studies: Platelet-rich plasma was prepared by centrifuging the anticoagulated blood at 150 g for 15 minutes. Blood samples were centrifuged at 3,330 g for 10 minutes to obtain platelet-poor plasma. After counting the platelets with the Coulter Counter (Model 2BI, Coulter Electronics, HighCal, Florida), the platelet-rich plasma was diluted with platelet-poor plasma to 200,000 platelets/mm^3. Platelet aggregation was monitored photometrically (Monitor IV Aggregometer, Helena Laboratories, Beaumont, Texas)[1,2]; platelet-rich and platelet-poor plasma absorptions were used to calibrate the 0 and 100% aggregation responses, respectively, of the instrument. To test platelet thresholds, 450 aliquots of platelet-rich plasma were heated at 37°C, and mixed at 1,000 rpm for 2 minutes with adenosine diphosphate (ADP) (Chronolog Corp., Havertown, Pennsylvania) or epinephrine (Parke-Davis, Morris Plains, New Jersey). The minimum concentration needed to produce an irreversible, biphasic increase in light transmission was considered the threshold value. To find the threshold, 6 concentrations of epinephrine (0.2 to 50 μM) and ADP (0.5 to 15 μM) were used in order of increasing concentration. The tracings obtained were then analyzed, and the lowest concentration of the aggregating agent to produce biphasic aggregation was evaluated as the index of platelet aggregability.

Platelet factor 4, β-thromboglobulin and D-Dimer: For assays of platelet factor 4, β-thromboglobulin and D-Dimer, enzyme-linked immunosorbent assays were used (Asserachrom, American Bioproducts).[4,9] The plasma samples were placed on microwell titer plates that were precoated with specific antibodies of the 3 proteins. An antiplatelet factor, anti-β-thromboglobulin or anti-D-Dimer peroxidase conjugate was added to form a sandwich. The color change was read on a microplate reader (Bio-Tek Instruments, Model El-305, Vincoski, Vermont) at 492 nm. Calibration curves were then constructed by standard solutions provided with the kit.

Thrombin–antithrombin III complexes: Thrombin–antithrombin III complexes in plasmas were affixed to antibodies to thrombin, which were precoated on the inner wall of a plastic tube of the enzymgnost kit (Behringwerke Marburg, Germany).[7] Peroxidase conjugated antibodies to antithrombin III were then added, which bind to the available free antithrombin III determinants. After removal of the free conjugate, the bound enzyme activity was measured by adding hydrogen peroxide and orthophenylenediamine. The color intensity was again read at 492 nm on the microplate reader. A reference curve was also obtained using a thrombin–antithrombin III complex standard plasma provided with the kit.

Statistical analysis: Data in the figures are presented as mean ± standard error. To assess whether overall differences were present, analysis of variance with repeated measures was performed. Log transformations were performed for some of the variables to adjust for unequal variances among the time points. Testing for all variables was performed at the 0.05 level. Pairwise comparisons were performed to compare differences for individual time points when overall significant variation or trends were detected during the 24-hour observation period. Pairwise testing was performed at the 0.01 level (instead of 0.05) to adjust for multiple comparisons.

RESULTS

Platelet function studies: Circadian changes in plasma levels of platelet release proteins, β-thromboglobulin and platelet factor 4 are summarized in Figure 1. Beta-thromboglobulin levels were highest at 3 P.M. on both days 1 (134 ± 32 IU/ml) and 2 (147 ± 29 IU/ml) of the study. Beta-thromboglobulin levels were lowest at 7

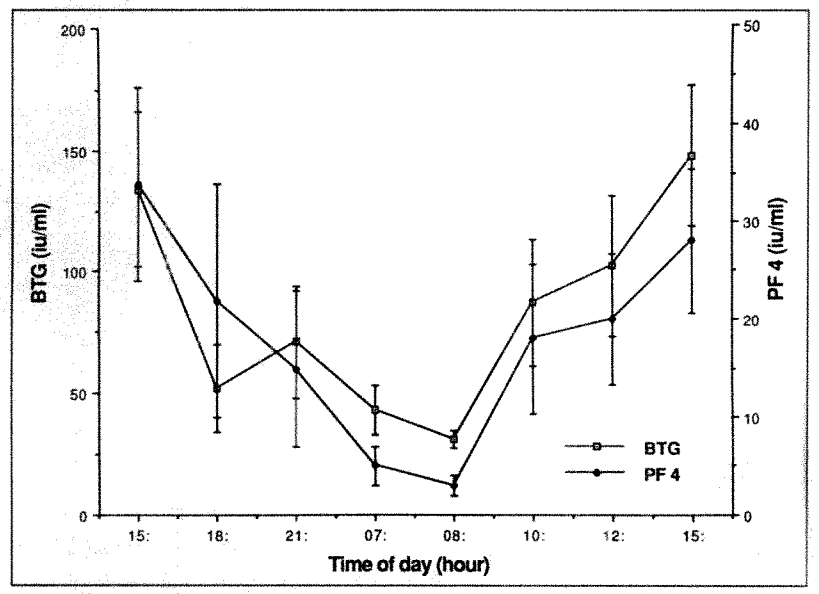


FIGURE 1. Circadian changes in plasma levels of platelet release proteins, platelet factor 4 (PF 4) and β-thromboglobulin (BTG). Circadian changes of in vitro platelet aggregation were associated with in vivo release of platelet factor 4 and β-thromboglobulin.

A.M. (43 ± 10 IU/ml) and 8 P.M. (31 ± 3.6 IU/ml) when patients were resting and in a supine position. Platelet factor 4 levels also increased with activity and peaked at 3 P.M. on both days 1 (34 ± 10 IU/ml) and 2 (28 ± 7.3 IU/ml). Platelet factor 4 levels were again lowest at 7 A.M. (5.0 ± 2.0 IU/ml) and 8 A.M. (3.0 ± 1.0 IU/ml). Circadian variation was detected for β-thromboglobulin ($p < 0.05$) and reached borderline significance for platelet factor 4 ($p < 0.06$). Furthermore, there were significant differences in β-thromboglobulin and platelet factor 4 levels obtained at 7 and 8 A.M. when compared with those at 3 P.M. ($p < 0.01$) on both days 1 and 2 of the study.

In vitro platelet aggregation responses to ADP ($p = 0.20$) and epinephrine ($p = 0.16$) are summarized in Figure 2. There were trends in circadian changes in in vitro aggregation response to epinephrine, with platelet aggregability being lowest at 7 and 8 A.M., and highest in the afternoon. These findings demonstrate platelet activation to have a circadian pattern with simultaneous trends of increase in both in vitro platelet aggregability in response to epinephrine and in vivo release of β-thromboglobulin and platelet factor 4 occurring at the same time of the day.

Markers of coagulation: An absence of circadian variation of thrombin–antithrombin III complexes ($p = 0.36$) and D-Dimer ($p = 0.44$) is displayed in Figure 3. An apparent increase in thrombin–antithrombin III complexes at 10 A.M. was due to abnormally elevated levels in 1 patient. Thus, in contrast to platelet function, circadian changes in activation of the coagulation system were not present in our study group.

DISCUSSION

The results indicate that platelet activation was lowest when patients were resting in a supine position and that it increased with activity. Changes in in vivo release of β-thromboglobulin and platelet factor 4, were accompanied by similar trends in in vitro response to platelet aggregating agent epinephrine. Circadian changes in

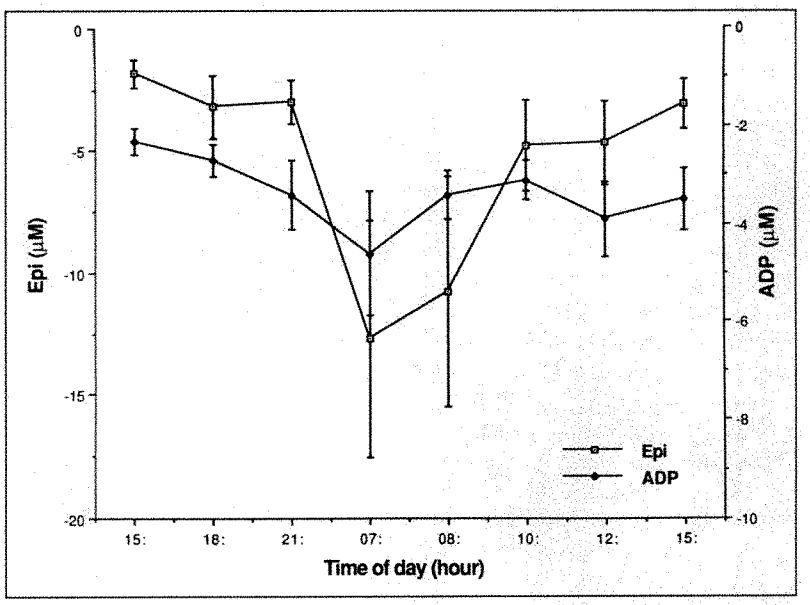


FIGURE 2. Circadian changes in threshold concentrations of adenosine diphosphate (ADP) and epinephrine (Epi) to produce irreversible biphasic platelet aggregation. In vitro platelet aggregability was lowest with patients resting and supine at 7 and 8 A.M., increased with activity and peaked at 3 P.M.

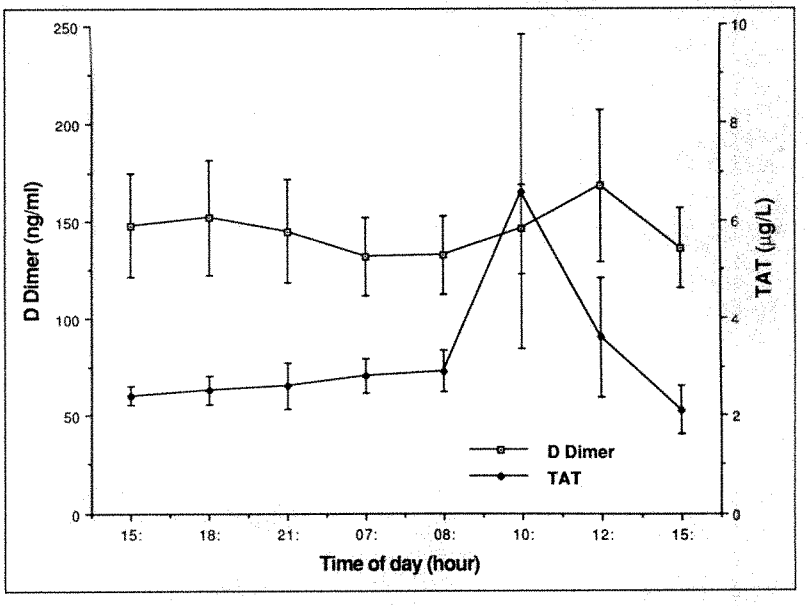


FIGURE 3. Absence of circadian changes in markers of thrombin activation, thrombin–antithrombin III complexes (TAT) and fibrinolysis, D-Dimers.

activation of coagulation (as detected by plasma levels of thrombin-antithrombin III complexes or D-Dimers) were not demonstrated.

A circadian variation of cardiac ischemic events has been documented for silent myocardial ischemia,[10] angina pectoris,[11] myocardial infarction[12] and sudden cardiac death.[13] A primary morning peak has been reported and a lesser prominent evening peak. Several physiologic changes occur with activity, which can trigger rupture of an atherosclerotic plaque, and production of coronary thrombosis. These changes include increases in serum catecholamines,[14] heart rate and blood pressure.[15] Clinical evidence that platelet activation may be an important trigger mechanism for coronary thrombosis comes from analysis of the Physician's Health Study.[16] Patients receiving aspirin had a 59.3% reduction in the incidence of myocardial infarction during morning hours compared with 34.1% during the remaining hours of the day.

Circadian variation of activation of platelet and coagulation has been investigated as a contributing trigger mechanism. In an earlier study, Tofler et al[1] showed a morning increase in in vitro platelet aggregability. In their subsequent study, platelet aggregability was shown to relate not particularly to the time of the day, but to assumption of an upright posture and to activity.[2] Results from our study confirm these latter observations, as platelet activation was related to activity with changes noted to increase in the morning hours after standing, and peaking at 3 P.M. However, other studies described in vitro and in vivo platelet aggregability to peak in the morning hours.[17,18] A consistent finding in all studies was that platelet activation is lowest when patients were resting. Differences occurred in the detection of peak platelet activation. In our study, a delayed peak may represent the gradual increase of platelet activation over the course of the day with continued activity. Alternatively, a bimodal peak in platelet activation could also exist as reported for cardiac events with morning and afternoon peaks in events.[19]

The absence of fibrinolytic tendency in the early morning hours is considered to be another potential contributing factor for the reported higher morning incidence of thrombotic cardiovascular events, as measured by tissue plasminogen activator and its inhibitor after a circadian rhythm.[20–22] We did not detect thrombin activation as fibrinolysis after a diurnal rhythm. It is possible that the ability to lyse a thrombus is reduced in the morning hours, but thrombin activation or fibrinolysis does not have diurnal variability in healthy subjects.

In conclusion, investigations to elucidate triggers for coronary thrombosis are important to understand mechanisms precipitating rupture of an atherosclerotic plaque. This study confirms circadian variation of platelet activation.

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Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution, therefore, should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

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Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients: Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Beta-Blocking Agents:*** A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism*.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28* times the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy: ***Pregnancy Category C:*** *Teratogenic Effects:* Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers: It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine, MSD) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (Incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL % N = 730	Placebo % N = 283
Peripheral Edema	22.3 (4.2)	3.5
Headache	16.6 (2.1)	10.6
Flushing	6.4 (1.0)	1.1
Dizziness	5.8 (0.8)	3.2
Upper Respiratory Infection	5.5 (0.1)	1.1
Asthenia	4.7 (0.1)	2.8
Cough	2.9 (0.0)	0.4
Paresthesia	2.5 (0.1)	1.8
Dyspepsia	2.3 (0.0)	1.4
Chest Pain	2.1 (0.1)	1.4
Nausea	1.9 (0.8)	1.1
Muscle Cramps	1.9 (0.0)	1.1
Palpitation	1.8 (0.5)	2.5
Abdominal Pain	1.8 (0.3)	1.1
Constipation	1.6 (0.1)	1.1
Diarrhea	1.6 (0.1)	1.1
Pharyngitis	1.6 (0.0)	0.4
Rhinorrhea	1.6 (0.0)	0.0
Back Pain	1.6 (0.0)	1.1
Rash	1.5 (0.1)	1.1

*Based on patient weight of 50 kg

*Based on patient weight of 50 kg

In the two dose response studies using PLENDIL® (Felodipine, MSD) as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related:

Adverse Effect	Placebo N = 121	5.0 mg N = 72	10.0 mg N = 123	20 mg N = 50
Peripheral Edema	2.5	13.9	19.5	36.0
Palpitation	0.8	0.0	2.4	12.0
Headache	12.4	11.1	18.7	28.0
Flushing	0.0	2.8	8.1	20.0

In addition, adverse experiences that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical studies (listed in order of decreasing severity within each category) and serious adverse events that occurred at a lower rate or were found during marketing experience (those lower rate events are in italics) were: *Body as a Whole:* Facial edema, warm sensation; *Cardiovascular:* Tachycardia, *myocardial infarction, hypotension, syncope, angina pectoris,* arrhythmia; *Digestive:* Vomiting, dry mouth, flatulence; *Hematologic: Anemia; Musculoskeletal:* Arthralgia, arm pain, knee pain, leg pain, foot pain, hip pain, myalgia; *Nervous/Psychiatric:* Depression, anxiety disorders, insomnia, irritability, nervousness, somnolence; *Respiratory:* Bronchitis, influenza, sinusitis, dyspnea, epistaxis, respiratory infection, sneezing; *Skin:* Contusion, erythema, urticaria; *Urogenital:* Decreased libido, impotence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also been studied as monotherapy in 680 patients with hypertension in U.S. and overseas controlled clinical studies. Other adverse experiences not listed above and with an incidence of 0.5 percent or greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointestinal pain; *Musculoskeletal:* Arthritis, local weakness, neck pain, shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respiratory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurred vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in <0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients*.)

Clinical Laboratory Test Findings: ***Serum Electrolytes:*** No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, *Renal/Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE: Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended initial dose is 5 mg once a day. Therapy should be adjusted individually according to patient response, generally at intervals of not less than two weeks. The usual dosage range is 5-10 mg once daily. The maximum recommended daily dose is 20 mg once a day. That dose in clinical trials showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function, because they may develop higher plasma concentrations of felodipine, should have their blood pressure monitored closely during dosage adjustment (see PRECAUTIONS). In general, doses above 10 mg should not be considered in these patients.

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Outcome and Complications of Prolonged Intraaortic Balloon Counterpulsation in Cardiac Patients

Jason M. Lazar, MD, Galal M. Ziady, MD, Stephen J. Dummer, MD, Mark Thompson, MD, and Robert J. Ruffner, MD

The risks and benefits of prolonged intraaortic balloon support for the management of refractory congestive heart failure and ischemia were studied in patients with end-stage heart disease who needed support for ≥5 days. Fifty-two insertions were performed by the percutaneous femoral route in 49 patients. The duration of insertion ranged from 5 to 46 days (mean 11.3). Clinical outcome including hemodynamic parameters and complications were recorded. Mean systemic arterial pressure did not change with balloon insertion (74 ± 19 vs 76 ± 11 mm Hg; p = not significant). Both the mean pulmonary artery and pulmonary arterial wedge pressures decreased (33 ± 8 to 26 ± 9 mm Hg [p <0.01], and 25 ± 8 to 17 ± 6 mm Hg [p <0.01], respectively). Over time, both parameters tended to increase, but remained significantly less than those before insertion. Cardiac index increased from 1.6 ± 0.4 to 2.2 ± 0.5 liters/min/m² on insertion and continued to increase to 2.7 ± 0.5 liters/min/m² (p <0.01) before removal. Definite balloon catheter infection developed in 7 patients, and hemorrhage occurred in an additional 7. Eleven patients had vascular compromise, with loss of pulse in 6, thrombosis of the femoral artery in 1, and pseudoaneurysm in 2. Lacerated femoral artery occurred in 1 patient, and mesenteric artery thrombosis in another. Twenty patients died from progressive heart failure and multiorgan system failure, and 19 survived to receive left ventricular assist device and heart transplantation. Only 10 patients were weaned off the balloon. In conclusion, prolonged intraaortic balloon pump support may be successfully used in end-stage heart disease.

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The intraaortic balloon has long been used to treat patients with cardiogenic shock and low-cardiac output syndrome. Circulatory support with balloon counterpulsation is most often used as a temporary therapy in settings of acute myocardial infarction, perioperative cardiac surgery and coronary angioplasty.[1,2,3,4] However, as the management of multiorgan system failure has improved, and clinical experience with the intraaortic balloon pump has increased, a number of patients are being mechanically supported for prolonged periods of time. Because the literature contains little data as to the efficacy of balloon assist for >4 days, we investigated the value and limitations of intraaortic balloon counterpulsation for ≥5 days in a group of patients with end-stage heart disease.

METHODS

We conducted a retrospective cohort analysis of intraaortic balloon insertions in patients admitted to the University of Pittsburgh Medical Center from 1987 to 1989. Patients included in the study needed the intraaortic balloon for ≥5 days. Most patients were referred for management of refractory congestive heart failure, and evaluation for heart transplantation candidacy. Fifty-two intraaortic balloon catheters were inserted in 49 patients using the percutaneous femoral artery technique. All insertions were performed in the operating room, coronary care unit or cardiac catheterization laboratory. All patients were maintained on inotropic support. In each patient, arterial oxygen saturation (as measured by pulse oximetry) was maintained at >95%. All patients received intravenous heparin (800 to 1,200 U/hour) to maintain a partial thromboplastin generation time between 50 and 70 seconds. The clinical outcome of each patient was recorded. Patients who survived had either received heart transplantation or placement of a left ventricular assist device, or were successfully weaned from the pump. To evaluate whether hemodynamic benefit would be sustained over time, mean pulmonary artery pressure, pulmonary artery wedge pressure, arterial blood pressure, and cardiac index were measured using a floating pulmonary artery catheter. Measurements were recorded immediately before and after insertion, and again before removal. Mean arterial blood pressure was obtained by either direct intraarterial measurement or sphygmomanometry. Hemodynamic variables were evaluated by a repeated measures design in consecutive patients. All complications related to use of the balloon pump were logged.

TABLE I Hemodynamic Measurements Recorded from Patients in the Study

	Before Insertion	Immediately After	Before Removal	p Value
Mean arterial pressure (mm Hg)	74 ± 19	74 ± 14	76 ± 11	NS
Mean pulmonary artery pressure (mm Hg)	33 ± 8	26 ± 9	30 ± 8	0.01
Pulmonary arterial wedge pressure (mm Hg)	25 ± 8	17 ± 6	21 ± 7	0.01
Cardiac index (L/min/m^2)	1.6 ± 0.4	2.2 ± 0.5	2.7 ± 0.5	0.001

All measurements are mean ± 1 SD.
NS = not significant.

TABLE II List of Complications

Complication	No. of Pts.
Infection	13 (27%)
Definite infection	7
Probable infection	4
Local site infection	2
Hemorrhage	7 (14%)
Vascular	11 (21%)
Loss of pulse	6
Femoral artery thrombosis	1
Pseudoaneurysm	2
Lacerated femoral artery	1
Mesenteric artery thrombosis	1
Rupture of balloon	2 (4%)

Definite balloon pump infection was defined clinically after balloon catheter removal if the same organism was isolated by blood culture and culture of the balloon catheter tip. An infection was considered probable when culture of the balloon catheter was negative, and blood cultures were positive, indicating bacteremia without an identifiable source. Local site infection was defined as drainage of the insertion site with positive culture. Hemorrhages were recorded if they resulted in the need for blood transfusion. All vascular complications were recorded as they appeared in the chart.

RESULTS

Patient characteristics: There were 49 patients (37 men and 12 women, age range 18 to 76 years, mean 54) needing balloon support for ≥5 days. Diagnostic categories included 30 patients with ischemic cardiomyopathy, 10 with idiopathic dilated cardiomyopathy, 1 with myocarditis, 4 with cardiogenic shock after surgery, and 4 others including 1 postpartum cardiomyopathy, 1 hemochromatosis, 1 Marfan's syndrome and 1 with presumed cardiomyopathy 5 years after orthotopic heart transplantation. Statistical analysis was performed using repeated measurements design.

Hemodynamics: Hemodynamic indexes (Table I) were measured immediately before and after insertion, and again before removal. Mean values are reported ± 1 standard deviation. Mean arterial pressure did not change over the 3 time periods. Mean pulmonary artery and pulmonary arterial wedge pressures initially decreased from 33 ± 8 to 26 ± 9 mm Hg and from 25 ± 8 to 17 ± 6 mm Hg, respectively, with insertion of the balloon pump. Although both parameters had increased during circulatory support to 30 ± 8 and 21 ± 7 mm Hg, respectively, they remained lower than before insertion ($p < 0.01$). The initiation of counterpulsation resulted in an increase of cardiac index from 1.6 ± 0.4 to 2.2 ± 0.5 liters/min/m^2. Over time, the cardiac index continued to improve (2.2 ± 0.5 to 2.7 ± 0.5 liters/min/m^2 [$p = 0.001$] before removal).

Complications: The various complications related to use of the balloon pump are listed in Table II. Culture isolates of the 7 patients who met criteria for definite balloon infection included 2 coagulase positive staphylococci, 2 coagulase negative staphylococci, 2 isolates of Pseudomonas aeruginosa, and 1 Klebsiella pneumonia. All definite infections occurred within 2 to 9 days (mean 5.4) of insertion of the balloon catheter. Two patients were thought at the time of treatment to have clinical evidence of septic shock. Four patients had probable balloon catheter infection including 3 with coagulase positive staphylococci, and 1 with both coagulase positive staphylococcus and enterococcus. Two additional patients exhibited local signs of infection. Hemorrhage necessitating blood transfusion occurred in 7 patients. Vascular compromise complicated the course of 11 patients. Six patients experienced loss of the distal pulse, needing reinsertion in the contralateral femoral artery; only 1 of these occurred >5 days after initiation of balloon support. One patient had a femoral artery thrombus, and another developed mesenteric artery occlusion (both documented by angiographic studies). Two patients had pseudoaneurysyms of the femoral artery, and 1 sustained a lacerated femoral artery. These latter 4 patients needed emergent surgical repair. Two balloons ruptured and were immediately replaced without consequence.

Clinical outcome: Twenty-nine patients (60%) survived, 10 were weaned off the pump, 8 received the assist device, and 11 underwent heart transplantation. Twenty patients (40%) died while on the pump. On the survival probability curve shown in Figure 1, the ordinate represents the percentage of patients alive on balloon counterpulsation at any one time who have not yet reached the favorable outcome of either heart transplantation, weaning from the pump, or placement of an assist device. On the seventh day of counterpulsation, there was a 75% chance of a patient achieving a desirable outcome, whereas at 17 days, this was still >50%. Similar on-pump mortality rates were observed in patients, whether supported for longer or shorter than a 2-week period (Figure 2).

DISCUSSION

There are several earlier reports on the clinical outcome of patients maintained on intraaortic balloon assist. In a multicenter study, Scheidt et al[5] observed that no patient in cardiogenic shock maintained on balloon support for >48 hours survived to be discharged. Hagemeijer et al[6] described prolonged survival in 7 of 10 patients with postinfarction heart failure mechanically supported for ≥10 days. Bolooki[7] reported long-term survival in 10 of 23 patients supported for ≥8 days. In

our study, 60% of patients lived to achieve favorable outcome. Of the 20 patients who died, multiorgan system failure and progressive cardiac dysfunction were the leading causes of mortality with or without associated infection. Although the probability of an individual dying while on the pump increased with the duration of balloon support, this probably reflected clinical deterioration rather than an adverse effect of long-term counterpulsation.

Intraaortic balloon pump counterpulsation has been reported to both increase systemic cardiac index by 10 to 15% and decrease left ventricular filling pressures by 30 to 40%.[8] In this study, insertion of the balloon pump resulted in a 34% increase in cardiac index, and a 32% decrease in mean pulmonary arterial wedge pressure. This marked improvement in hemodynamic profile may be related to a poor baseline level of ventricular function in the cohort. Over time, cardiac index continued to increase. These observations vary somewhat from those of other investigators who suggested that the hemodynamic improvement of balloon support is attenuated in 2 to 3 days.[9,10]

Iskandrian et al[11] also evaluated the effect of balloon pump support on left ventricular function. An improvement in left ventricular ejection fraction (measured by radionuclide ventriculography) was demonstrated in patients with unstable angina, but not in those with postinfarction heart failure. Alternatively, Weiss et al[12] reported a significant increase in left ventricular ejection fraction in all 15 patients with acute myocardial infarction and cardiogenic shock. Ejection fraction was not used to assess the effect of afterload reduction on left ventricular function in our study. However, cardiac function (as inferred from augmented cardiac output and lowered filling pressures) improved in both ischemic and nonischemic patients.

Most complications related to the intraaortic balloon pump were infectious and vascular. Seven patients met criteria for definite infection, and 4 others became bacteremic without an apparent alternative source. All definite infections occurred by the ninth day of balloon support. After 5 days, the risk of infection had not significantly increased. This finding, although differing with other reports describing the incidence of infection to be related to the duration of counterpulsation,[13] suggests the occurrence of infection at the time of insertion rather than during the course of circulatory support. A high prevalence of gram negative pathogens were isolated on blood and catheter-tip culture. Therefore, empiric antibiotic therapy for suspected pump infection needs broad spectrum antibiotic coverage.

The vascular complication rate is similar to that of reports of shorter duration balloon pump support.[14-16] Women were not found to be at increased risk of vascular occlusion, as previously suggested.[17,18] However, the small numbers of both female patients and vascular events limit the statistical power to detect such differences. As with infection, there appeared to be no relation between duration of insertion and the risk of vascular compromise. The retrospective design of this study poses some inherent limitations. The cohort was not compared with medically treated matched control subjects. Data collection remained highly dependent on documentation by a busy physician and nursing staff.

Hemodynamic deterioration may complicate attempts at weaning, thereby denoting balloon dependency.[19] With improved management of multiorgan system failure, patients may be supported for prolonged periods of time. Some doctors routinely use prolonged balloon support for specific clinical cases, such as after cardiac surgery in patients with heart failure.[10] Our data suggest that prolonged intraaortic balloon pump counterpulsation may benefit patients with cardiac disease. Because hemodynamic stability appears to be maintained during long-term circulatory assist, patients may be supported until heart transplantation or placement of assist device, or until sufficient time has been allowed for myocardial recovery. Although infectious and vascular complications related to use of the balloon pump occurred in the majority of patients, they appear to be

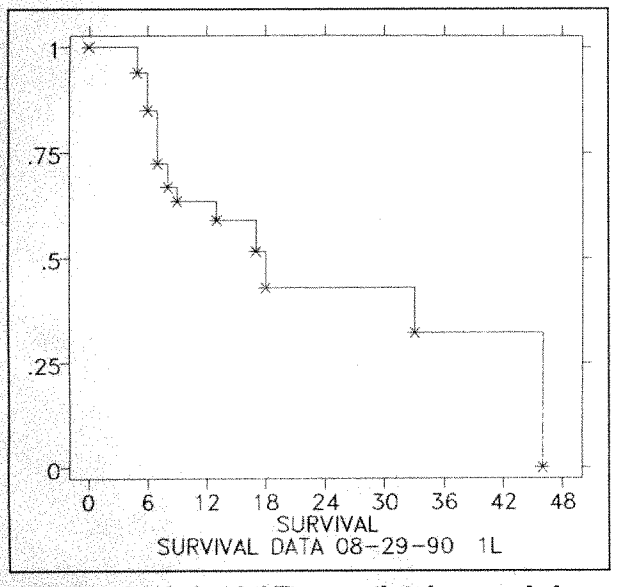


FIGURE 1. Survival probability curve that shows survival analysis of all patients over longest period that balloon was left in (46 days).

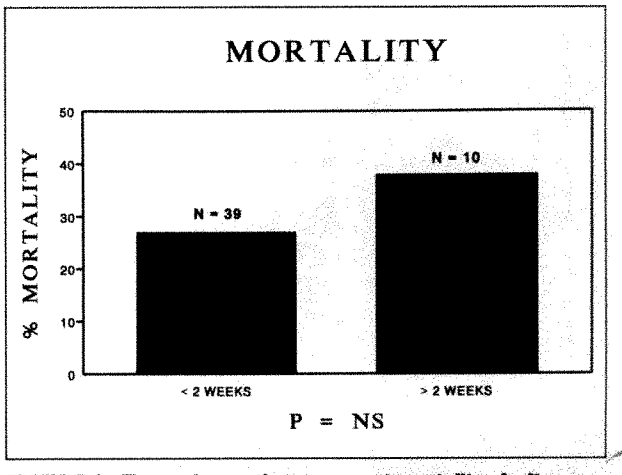


FIGURE 2. *Two columns* that represent mortality. *Left* represents patient mortality (30%) with intraaortic balloon for ≤2 weeks (39 patients). *Right* represents mortality (38%) with balloon insertion for >2 weeks (10 patients). NS = not significant.

unrelated to the duration of insertion and have little impact on overall mortality.

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Evaluation of the Implantable Cardioverter Defibrillator in Survivors of Cardiac Arrest: The Need for Randomized Trials

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The implantable cardioverter defibrillator (ICD) is an important and unique new method of potentially preventing sudden death due to ventricular arrhythmia, and it is increasingly being used to treat survivors of cardiac arrest (not associated with acute myocardial infarction). Recently, the North American Society for Pacing and Electrophysiology[1] stated that the ICD is indicated for patients with sustained ventricular tachycardia and fibrillation, except those who become noninducible at electrophysiologic drug testing. However, the effectiveness of the ICD for reduction of both sudden death and overall mortality has not been conclusively demonstrated. Some commentators[2-4] stated that based on nonrandomized studies in survivors of sudden death, the effectiveness of the ICD is "obvious" and essentially proven, rendering a randomized trial unethical. It is reasonable to accept that a randomized trial is neither necessary, nor even perhaps ethical, when the benefits of a new treatment are of very great magnitude, or when the outcome is uniformly poor with conventional therapy, and the benefits are moderate. However, in other circumstances, nonrandomized comparisons can potentially be very misleading, and great caution is needed when adopting a new treatment in the absence of data from randomized trials. The question that needs to be answered is not whether the ICD can effectively terminate malignant arrhythmias that would otherwise be fatal, because this has been amply documented by ambulatory electrocardiographic monitoring.[5-8] The relevant clinical question is whether the ICD reduces overall mortality among survivors of cardiac arrest (not associated with myocardial infarction) compared with the best medical therapy. The answer to the latter question is complex, because it must account for multiple issues including perioperative mortality, concurrent competing risks of death from pump failure and acute ischemia, the potential risks and benefits of medical therapy, and the possibility that the ICD may only change the mode of death (in some patients) from arrhythmic to nonarrhythmic. The only way to reliably answer this question currently is by means of a randomized trial.

Patients who are resuscitated from cardiac arrest have substantial degrees of left ventricular dysfunction and often have myocardial ischemia. In such patients there are many potential causes of cardiac death, and there is a practical limit to the reduction in mortality that a purely antiarrhythmic treatment can achieve even if it is completely effective in controlling malignant tachyarrhythmia. Although cardiac arrest survivors have a high risk of recurrence of a potentially fatal arrhythmia, they are also at high risk of a nonarrhythmic death. In several follow-up studies of patients treated medically for severe sustained ventricular tachycardia or recent cardiac arrest, 20 to 68% of all deaths were sudden.[9-14] This suggests that even complete abolition of sudden death by the ICD would probably not reduce overall mortality by >50%. However, it is likely that not all sudden deaths are due to a tachyarrhythmia. Luu et al[15] showed that in patients with poor ventricular function, a high proportion of sudden death is due to asystole. Even in cases of ventricular tachycardia or fibrillation, the ICD may not be successful in patients with extensive ischemia. Davies and Thomas[16] reported a very high occurrence (74%) of intraluminal and intraintimal thrombosis due to plaque-fissuring in patients dying suddenly with ischemic heart disease. These data suggest the possibility that some episodes of ventricular fibrillation are subsequent to myocardial ischemia or infarction, or both. These considerations suggest that the rate of salvage by ICD is likely to be partial, and this makes the possibility of complete abolition of sudden death by any purely antiarrhythmic approach unlikely. The perioperative mortality of 1.5 to 9.6%[7,8,17-22] for implantation of the ICD will also reduce some of the overall benefit of ICD. Given that sudden deaths are likely to account for less than half of all deaths in these patients and that the rate of salvage of sudden death by ICD will only be partial, it is unlikely that the reduction in overall mortality by ICD will be >33%. This is certainly more modest than the 80 to 90% reduction that was originally suggested by uncontrolled studies. Benefits of approximately a one third reduction in mortality cannot be reliably detected or excluded by observational studies owing to the inherent biologic variability in mortality rates, and to differences in patient characteristics and cotherapy. Such benefits can only be confirmed or rejected by a randomized trial.

Previous studies: There are several types and sources of evidence currently available for evaluation of the efficacy of the ICD in survivors of cardiac arrest (not associated with acute myocardial infarction) (Table I). Relatively weak evidence derives from follow-up studies[14,18,20] without a comparative group. These can be compared with other follow-up studies of relatively similar patients receiving different treatments, but the potential for bias is great. For example, Winkle et al[20]

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TABLE I Overview of Studies Evaluating the Efficacy of the Implantable Cardioverter Defibrillator on Survival: Different Approaches and Their Limitations (modified from reference 29)

Type of Study	Results	Limitations
1. Comparison of series with ICD versus separate series of historical control subjects from same or another center	Claims for reduced sudden death. However, lower nonsudden death with ICD is apparent in some series, suggesting biases in patient selection[20]	1. Marked differences in patient selection, concomitant therapy and CABG surgery 2. Biases due to differences in time from cardiac arrest to entry into study (e.g., may be longer in studies of ICD, so highest risk patients may have died before entry)
2. Comparison of actual with "projected" sudden death rates based on number of "appropriate" shocks	Claims for reduced sudden death[3,7,22,23]	1. Validity of ascertaining "appropriate" shock dubious 2. Large number of shocks may be inappropriate 3. Reversible episodes of VT or fast AF may be shocked
3. Comparison with historical matched control subjects within same institution	Reduced sudden death, but increase in deaths due to heart failure. Difference in mortality only apparent for approximately 2 years[13]	1. No assurance that all prognostic features matched 2. No assurance that all other treatments similar 3. Biases due to differences in time from cardiac arrest to entry into study
4. Comparison of concurrent, unmatched, nonrandomized groups receiving and not receiving ICD	Reduced sudden death in 2 studies. No effect on overall mortality in 3 studies[21,25,27]	Same as for type 3 studies, except differences in cotherapy less likely
5. Concurrent matched control subjects	No study	No guarantee that selection or referral biases can be avoided
6. Concurrent randomized control subjects	Preliminary results of an ongoing study shows no benefit on total mortality, but apparent effect on sudden death[17]	Primary end point should be cardiac or total mortality to avoid classification biases
7. Concurrent randomized control subjects, use of devices that can record rhythm at same time of ICD discharge	No study	Same as above

AF = atrial fibrillation; CABG = coronary artery bypass graft surgery; ICD = implantable cardioverter defibrillator; VT = ventricular tachycardia.

reported their experience with 270 patients with life-threatening arrhythmias who received ICD implants for sustained ventricular tachycardia or aborted sudden death. The 1- and 3-year event rates were 1 and 4%, respectively, for sudden death, and 8 and 18%, respectively, for overall mortality. These data can be compared with those from a study[10] of 462 patients who were treated with amiodarone for the same indication, and who had a similar left ventricular ejection fraction and spectrum of presenting arrhythmias (Table II). In this comparison there appears to be a dramatic reduction in the 1-year risk of sudden death (from 9% in the series treated with amiodarone to 1% in the series with the ICD). However, there is also a very large reduction in overall mortality (from 24 to 8%), only half of which is explained by the absolute reduction of 8% in sudden death. In fact, as many nonsudden deaths appear to be prevented by the ICD as sudden deaths. It is likely that the marked differences in the rates of nonsudden and sudden deaths are a reflection of the fact that inherently lower risk subjects were chosen to receive an ICD than those who received amiodarone. It is possible but less likely that amiodarone increased nonsudden death. This highlights the problems and very real potential for bias, if one compares outcomes when the treatments are not allocated randomly.

TABLE II Comparison of Actuarial Mortality After Treatment of Life-Threatening Arrhythmia with ICD or Amiodarone in Two Different Follow-Up Studies

Follow-Up Time	1 Year	3 Years	5 Years
ICD (Winkle et al)[20]			
No. of pts.	188	69	12
Sudden death	1%	4%	4%
Nonsudden death	7%	14%	22%
Overall death	8%	18%	26%
Amiodarone (Herre et al)[10]			
No. of pts.	261	101	13
Sudden death	9%	15%	21%
Nonsudden death	15%	28%	41%
Overall death	24%	43%	62%

ICD = implantable cardioverter defibrillator.

A second type of study has used the discharge of the ICD under appropriate circumstances as a surrogate end point, assuming that the patient would have died had the ICD not been implanted.[3,7,22–25] The observed mortality can then be compared with an assumed mortality estimated by counting appropriate shocks. For example, Fogoros et al[3] reported the follow-up of 119 patients with malignant arrhythmia who received ICD. Actual versus projected survival rates at 1, 2 and 3 years were 97, 90 and 85% vs 59, 39 and 31%, respectively ($p < 0.001$). All studies using this methodology appear to indicate a sizable benefit for ICD therapy, but these results should be interpreted very cautiously. Not only is it possible for nonsustained ventricular or supraventricular tachycardia to mimic an appropriate shock, but many patients in these studies demonstrated the ability to survive (at least once) an episode of sustained ventricular tachycardia. Furthermore, medical therapy is not standardized, as some patients have received no medical treatment, and others have received

potentially harmful therapy (such as Vaughan-Williams class I drugs). Thus it is virtually certain that these studies overestimate the benefit of ICD. However, the degree to which the benefits may be overestimated is open to conjecture.

A third type of study compares 2 groups of patients from 1 center allocated to receive or not receive ICD in a nonrandomized manner. Fogoros et al[26] reported that owing to a temporary lack of availability of the ICD, 29 patients with sustained ventricular tachycardia or fibrillation were treated with amiodarone alone and were compared with 21 other patients (who appeared to be well-matched) who received both amiodarone and the ICD. The group receiving amiodarone alone had a 24-month actuarial risk of sudden death of 31% compared with 0% for those receiving ICD plus amiodarone. However, nonsudden death was considerably more frequent in the patients receiving amiodarone alone (14 vs 5%), which (as discussed previously) suggests the possibility of an imbalance in baseline risk factors that were not measured or documented in the 2 groups. More recently, Pinski et al[21] reported the follow-up of 77 patients from 1 institution for whom the ICD was recommended for treatment of drug refractory or noninducible malignant arrhythmia. Fifteen patients (19%) refused ICD implant, and 14 of these received amiodarone (either alone or with a Vaughan-Williams class I drug). Baseline characteristics were apparently similar between the 2 groups. Perioperative mortality was 6% in the ICD group. Survival at 18 months was not significantly different (84% with and 78% without ICD).

Crandall et al[27] reported the follow-up of 196 consecutive sudden death survivors in whom ventricular tachycardia could not be induced by programmed stimulation. Selection of the ICD was nonrandom; 98 received ICD and 98 did not. There was no difference between the groups in any predictors of outcome, except age (which was lower for ICD patients). The 2-year risk of sudden death was lower for ICD patients (3 vs 11%; $p = 0.02$), but overall survival was similar for the 2 groups (90 with and 88% without ICD). Perioperative mortality was 3%. Although the imbalance in nonsudden death could be due to a selection bias against ICD, it is also possible that the survival benefit owing to prevention of arrhythmic death was offset by continuing mortality due to other causes (e.g., heart failure).

To summarize, some of these nonrandomized studies indicate that the ICD improves survival. However, it appears that there were substantial biases in patient selection that generally led to lower risk patients receiving ICD therapy. The more recent studies in which more careful methodology was used suggest that the overall benefit from ICD therapy in these patients may be somewhat modest owing to substantial competing risks of deaths from other causes.

Present study: The importance of the current report by Newman et al[13] is that it is the first fully published study that has formally attempted to compare ICD-treated patients with a matched control group. This retrospective case control study from 1 center compared the first 60 ICD recipients with 120 control subjects who did not receive the ICD. They were matched for age, left ventricular ejection fraction, presenting arrhythmia, underlying heart disease and drug therapy status. Sudden deaths were reduced by 50% with the ICD (10 vs 5%; $p < 0.01$), and 3-year actuarial mortality was reduced by 31% (51 vs 35%; $p < 0.01$). The 5-year actuarial survival curves differed significantly. Although this study was small (60 ICD patients), it provides support for the use of ICD in patients with sustained ventricular tachycardia and in survivors of sudden death. Although the case control method reduces some of the potential for bias in patient selection for the different therapies, there is still potential for there to be imbalances between the 2 groups. The 5 variables chosen for matching are very important predictors of outcome. However, other less identifiable factors that determined who would receive ICD (including intuition of the physician) cannot be controlled, and some of these factors could substantially influence outcomes. It is also interesting to note that 80% of all deaths were nonsudden (Table III). As with several previous reports, there was an apparent reduction in nonsudden deaths by the ICD. The reduction in nonsudden death (39 vs 17%) actually exceeds that in sudden death (10 vs 5%). Considering that medical therapy was well-matched between the 2 groups, the difference in nonsudden death strongly suggests that in some way the ICD patients were inherently less sick. As the investigators pointed out, the 2.8-year lag between the treatment of the control and ICD patients may have resulted in greater use of some beneficial interventions such as angiotensin-converting enzyme inhibitors, aspirin and coronary revascularization in the ICD patients. This study is an important advance methodologically over most previous reports, but it is still possible that systematic differences in patient characteristics, and differences in concomitant treatment could have accounted for part of the benefit seen.

TABLE III Causes of Death in Newman et al[13]

Cause of Death	ICD (n = 60)	Control Subjects (n = 120)
Sudden death	3 (5%)	12 (10%)
Nonsudden death	10 (17%)	47 (39%)
Overall mortality	13 (22%)	59 (49%)

ICD = implantable cardioverter defibrillator.

Need for randomized trials, and some forthcoming studies: A critical review of the currently available data does not provide reliable evidence of the efficacy of the ICD to improve overall survival. As the methods of evaluation have become more rigorous and hence more reliable, the benefits of the ICD (especially on total mortality) appear modest. In fact, the only data available from a randomized trial have shown little difference in overall mortality. The Hamburg Cardiac Arrest Study[17] is the first randomized controlled trial of ICD therapy in sudden death survivors, and it has published interim data on 139 patients randomized to receive either ICD, amiodarone, propafenone or metoprolol (followed for a mean of 11 months). The ICD reduced the rate of sudden death to 0 compared with 9% receiving

amiodarone, and 11% each for metoprolol and propafenone. Overall mortality was not different between ICD and drug therapy (14% ICD, 14% metoprolol, 15% amiodarone and 20% propafenone). However, because of the small size of the study, a reduction in overall mortality of approximately 30% cannot be reliably excluded.

The burden of pump dysfunction and coronary ischemia in survivors of sudden death, and the results of more recent studies suggest that the benefit of the ICD in overall mortality will not be large and is unlikely to exceed 33%. Mortality reductions in this range have been seen with 2 antiarrhythmic drugs in postmyocardial infarction survivors. An overview of the β-blocker, postmyocardial infarction trials reported a 23% reduction in mortality ($p < 0.00001$).[28] A meta-analysis of randomized trials of amiodarone after myocardial infarction indicated a reduction in mortality of 34% (95% confidence interval 54 to 7%; $p < 0.02$).[29] These data indicate that the benefits of the ICD should be demonstrated to be larger or additional to the best available medical management. This can only be achieved by conducting randomized trials (that are sufficiently large) comparing the ICD with (or in addition to) the best alternate therapy (perhaps a combination of β-blockers and amiodarone). Such trials are ethically justified even in high-risk patients, because of the weak data supporting the overall clinical benefits from the ICD, its high costs, the significant morbidity and mortality associated with its implantation, and the availability of at least two relatively simpler forms of therapy with substantial proof of efficacy.

In addition to the Hamburg Study, a randomized trial of ICD therapy is currently underway in Canada (Canadian Implantable Defibrillator Study [CIDS]). In this study survivors of cardiac arrest, and patients with malignant sustained ventricular tachycardia are randomized to receive or not receive the ICD. All non-ICD patients receive amiodarone. A quarter of the anticipated recruitment of 400 patients is completed. No interim results are available. The National Heart, Lung, and Blood Institute has recognized the need for evaluation of the ICD in survivors of cardiac arrest and approved funding of a study that aims to ultimately recruit approximately 700 to 800 patients. Reliable evaluation of the ICD will have to await the results of the aforementioned trials in high-risk subjects, and the results of several other trials in relatively lower risk subjects (e.g., patients who have not yet had a cardiac arrest, but have characteristics that increase the risk of such an event).

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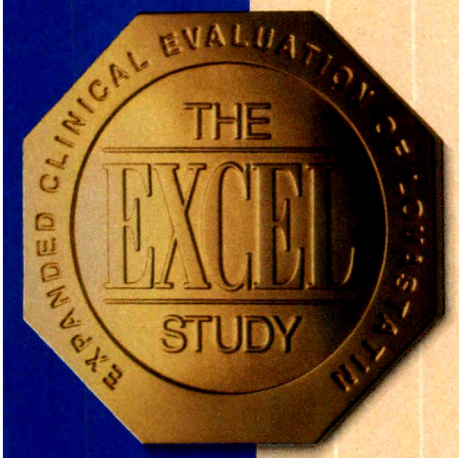
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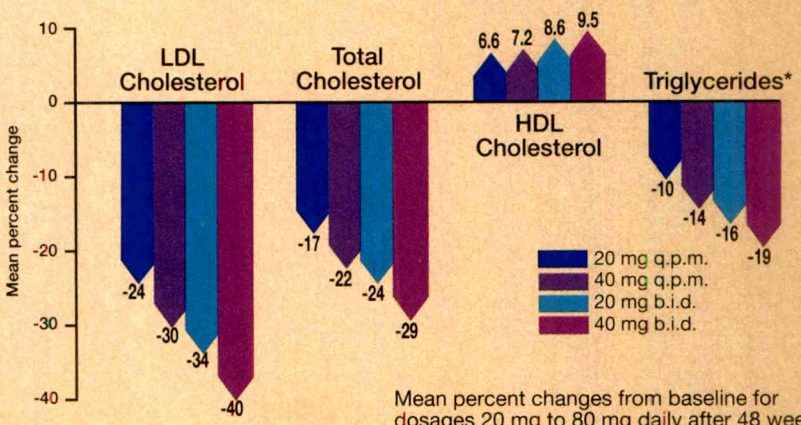
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For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

For a brief summary of Prescribing Information, please see the next page of this advertisement.

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MEVACOR®*
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CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation.

Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction:* Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least 1 year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity in the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and, in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated CPK levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 5 patients (0.1%) taking lovastatin alone (1 at 40 mg q.p.m. and 4 at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels >10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General:* Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in the full Prescribing Information).

Lovastatin may elevate CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with these rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin-treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than 2-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Because lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on an mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR® [Lovastatin].)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) the human exposure based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose). MEVACOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking MEVACOR, it should be discontinued, and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences that were rated by the investigator as possibly, probably, or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences: Adverse experiences reported in patients (%) treated with MEVACOR (n=613) in controlled clinical studies are: *Gastrointestinal:* constipation, 4.9; diarrhea, 5.5; dyspepsia, 3.9; flatus, 6.4; abdominal pain/cramps, 5.7; heartburn, 1.6; nausea, 4.7; *Musculoskeletal:* muscle cramps, 1.1; myalgia, 2.4; *Nervous System/Psychiatric:* dizziness, 2.0; headache, 9.3; *Skin:* rash/pruritus, 5.2; *Special Senses:* blurred vision, 1.5; dysgeusia, 0.8.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9%, and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Clinical Adverse Experiences: MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240 to 300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably, or definitely drug related in ≥1% of any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

		MEVACOR			
	Placebo (n=1,663) %	20 mg q.p.m. (n=1,642) %	40 mg q.p.m. (n=1,645) %	20 mg b.i.d. (n=1,646) %	40 mg b.i.d. (n=1,649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.9	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably, or definitely drug related in 0.5 to 1% of patients in any drug-treated group are listed below. In all these cases, the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE: After oral administration of MEVACOR to mice, the median lethal dose observed was >15 g/m².

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information for dose-response results).

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically, and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY in the full Prescribing Information and WARNINGS, *Skeletal Muscle*).

For more detailed information, consult your MSD Representative or see the Prescribing Information.

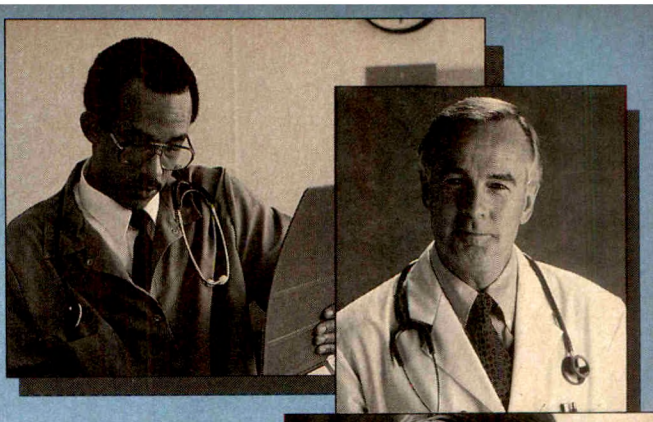
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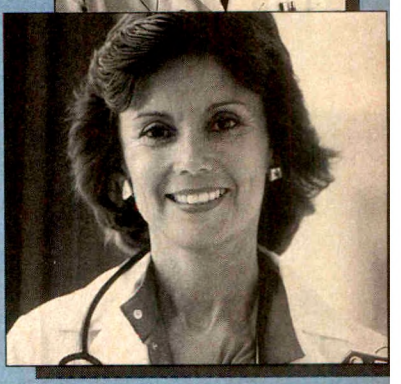
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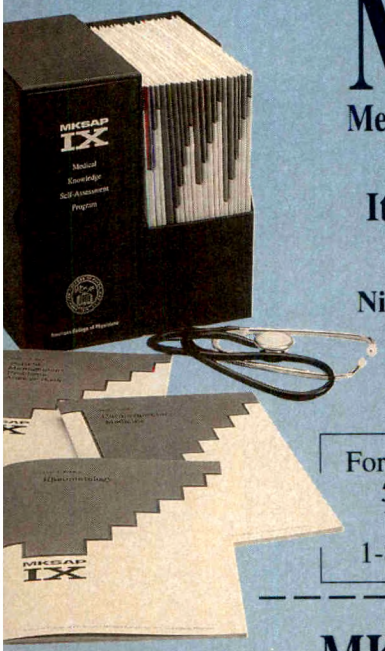
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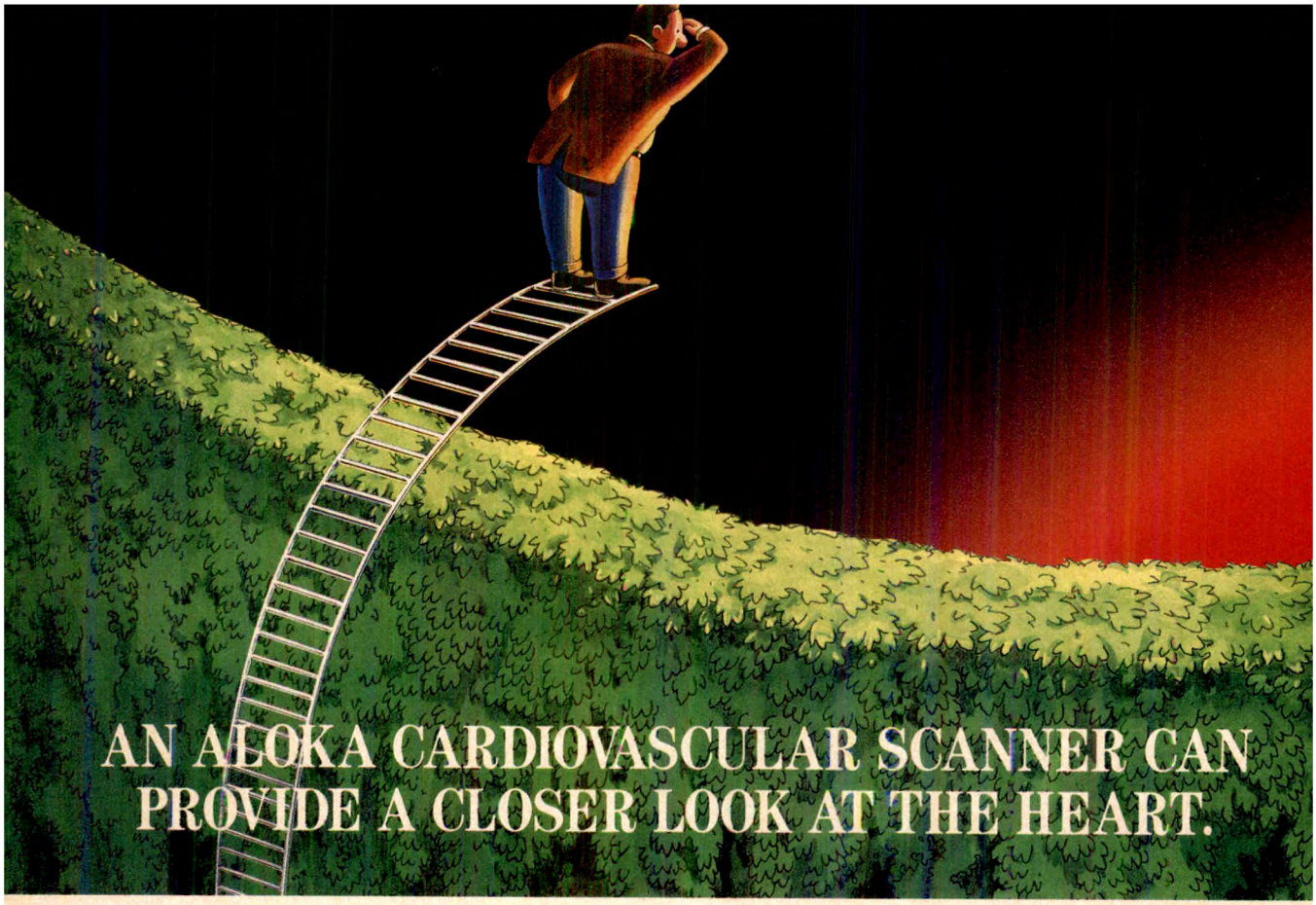
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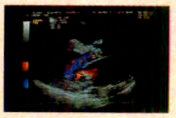
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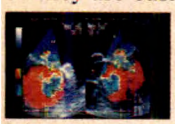
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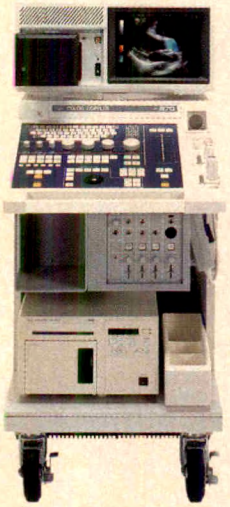
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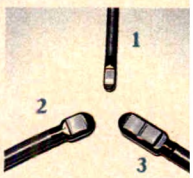
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Meta-Analysis of the Effectiveness of Prophylactic Drug Therapy in Preventing Supraventricular Arrhythmia Early After Coronary Artery Bypass Grafting

Peter R. Kowey, MD, Joan E. Taylor, LPN, Seth J. Rials, MD, PhD, and Roger A. Marinchak, MD

There has been considerable interest in evaluating the usefulness of drug therapy in patients who undergo operative coronary revascularization procedures to prevent the development of supraventricular tachyarrhythmia after surgery.[1,2] Much concern stems from the fact that postoperative atrial fibrillation prolongs hospitalization, thus increasing the cost of this already expensive and frequently used procedure.[3] There is an attendant risk of severe complications of atrial fibrillation (most importantly stroke), which necessitates anticoagulation in a significant percentage of these patients.[4] Furthermore, the medications used to convert atrial fibrillation to sinus rhythm and to prevent recurrence are not innocuous, and arguably may increase the risk of death during follow-up.[5] For all these reasons, it is worthwhile to investigate whether medication, administered either before or immediately after the procedure, may prevent atrial fibrillation and other supraventricular arrhythmias.

Currently, the most frequently used medications for preventing the development of supraventricular tachyarrhythmia after surgery are β-adrenergic blocking agents and digitalis. Several studies have been undertaken to study their effectiveness.[6–17] Unfortunately, no consensus opinion has been reached regarding their relative usefulness. In fact, there has been considerable inconsistency of results. Consequently, in most hospitals there is no uniform policy regarding their routine use. Much of the problem occurs because of the small number of patients in each study, and the relatively modest treatment effect in most of these. The technique of meta-analysis can often help to interpret this kind of diverse data.[18] By combining the information obtainable from a number of small but well-done studies, it is possible to draw some conclusions about the relative magnitude of treatment effect. We reviewed 12 full-length reports in which digitalis or β-blocker therapy, or both, was compared with control therapy, combined the information and herein report the results.

We conducted a review of reports (in English) that were published in the last 15 years. We examined each of these reports to select those that fulfilled a number of criteria, including incorporation of a placebo control, adequate numbers, exact delineation of treatment and dose, and careful reporting of outcome. We included only those articles that specified the type of supraventricular arrhythmia that occurred. In the vast majority, the arrhythmia identified was atrial fibrillation, but in rare cases, the investigators did not provide a full characterization. We also excluded reports that did not provide sufficient information to conclude that all arrhythmias could have been detected after surgery. All studies in which other antiarrhythmic drugs could have been used were also excluded, as were those in which other procedures (other than coronary revascularization) were not interdicted. Twelve of 95 screened reports met all these criteria and are the subject of this report. Two articles incorporated 2 treatment arms; data from these groups have been handled separately, yielding 14 sets of data for analysis. Seven series examined β blockers, 5 digitalis, and 2 the combination of digitalis and β-blockade. Results were tabulated, then combined. A chi-square method was used for comparisons of proportions, with an adjustment for multiple comparisons.

A list of the articles included in this report, together with the number of patients, drug administered and dose, appears in Table I. The total number of patients in all 12 trials was 2,482. Of these, 1,311 received placebo therapy, 675 β blockers, 357 digitalis and 139 a combination of β blockers and digitalis. The mean age of the entire cohort was 55 years, with a man:woman ratio of 4.5:1.

The incidence of arrhythmia after surgery for each main treatment group is shown in Table II. It is clear that of the 3 treatment options, the only one with no significant effect and only a trend toward benefit was digitalis. β blockers when used alone or in combination with digitalis reduced the incidence of supraventricular arrhythmia to a significant extent. Combination therapy was better than β blockers alone ($p < 0.005$), which was in turn better than digitalis alone ($p < 0.02$).

Supraventricular arrhythmia can have significant impact on the management of patients after coronary revas-

TABLE I List of Trials

Study Group	Drug Listed	Daily Dose (mg)	Active Therapy (n)	Control (n)
Daudon et al[6]	Acebutolol	400	50	50
Shafei et al[7]	Propranolol	30	343	537
Matangi et al[8]	Propranolol	20	82	82
Mohr et al[9]	Propranolol	20–40	37	48
Mills et al[10]	Propranolol/ digoxin	40/0.25	89	90
Rubin et al[11]	Propranolol	80	37	40
	Digoxin	0.25	46	
Stephenson et al[12]	Propranolol	40	87	136
Roffman and Fieldman[13]	Propranolol/ digoxin	60/0.25	50	63
	Digoxin	0.25	59	
Janssen et al[14]	Metoprolol	150	39	50
Johnson et al[15]	Digoxin	0.25	54	66
Tyras et al[16]	Digoxin	0.25	61	79
Csicsko et al[17]	Digoxin	0.25	137	270

From the Lankenau Hospital and Medical Research Center, and Thomas Jefferson University, Philadelphia, Pennsylvania. This study was supported in part by a grant from the Mary L. Smith Charitable Leed Trust, Philadelphia, Pennsylvania. Dr. Kowey's address is: Lankenau Medical Office Building East, Suite 556, 100 Lancaster Avenue, West of City Line, Wynnewood, Pennsylvania 19096. Manuscript received August 26, 1991; revised manuscript received and accepted December 2, 1991.

TABLE II Incidence of Arrhythmia After Surgery

No. of Trials	No. of Pts.	Mean Age (yr)	M/F Ratio	Control Subjects SVA (n) Total	Control Subjects (%)	Treatment SVA (n) Total	Treatment (%)
Group 1: β Blocker							
7	1,418	55	5.1:1	150/743	(20.2%)	66/675	(9.8%)*
Group 2: Digoxin							
5	875	54	3.6:1	99/518†	(19.1%)	55/357	(15.4%)
Group 3: β Blockers and Digoxin							
2	292	55	5.6:1	45/153†	(29.4%)	3/139	(2.2%)*

*$p < 0.001$ compared with control subjects.
†103 placebo patients were counted twice because 2 studies incorporated 2 active and 1 control treatment arm.
Group-wise comparison: groups 1 and 2, $p < 0.005$; groups 1 and 3, $p < 0.01$; groups 2 and 3, $p < 0.005$.
SVA = supraventricular arrhythmia.

cularization procedures. Length of stay, and duration of time on a monitored unit are significantly increased. Furthermore, class I antiarrhythmic drugs are frequently needed (with all of their attendant risks). In the control population in this analysis, atrial arrhythmias occurred in >20% of patients, making it the most frequent complication of the most common form of major surgery performed in the United States. It is a costly arrhythmia, increasing the price of coronary revascularization procedures by >16% or $8,000/case.[3] Currently, there are no convincing data to prove that any clinical factors (considered alone or in combination) can distinguish patients who are at highest risk and should be targeted for therapy.[2] Consequently, if therapy is to be used, all patients would need to be included.

The most frequently studied drugs for the prevention of atrial arrhythmias after surgery are digitalis and β blockers.[6–17] There are several reasons for these choices. By their effect on atrioventricular nodal refractoriness and conduction, both agents slow the ventricular response to atrial fibrillation, and can be used to terminate and prevent reentrant supraventricular arrhythmias. Many clinicians believe that digitalis and β blockers have an atrial antifibrillatory effect in conventional doses, although this has been disputed recently, especially in the case of digitalis.[19] Digitalis has been favored because of its positive inotropic effect, although β blockers have proved to be safe in the trials in which they were tested, probably because they were used in low doses, and patients were selected carefully. The use of more potent class I drugs for prophylaxis has been attempted with some salutary results.[20–22] This practice has been eschewed by most clinicians owing to the substantial risks of using these agents in patients who have had recent coronary artery surgery, many of whom have had recent major ischemic events.

Although most clinicians would agree that the use of a drug such as a β blocker or digitalis to prevent atrial dysrhythmias may be worthwhile, few programs actually incorporate drug therapy into their surgical protocols for this purpose. This is largely because of the conflicting results in trials published to date. For example, 2 digitalis trials included in our analysis (Johnson et al[15] and Tyras et al[16]) used the same dose of digitalis, had similar sample sizes and patient characteristics, and arrived at opposite conclusions. A likely cause for this discrepancy is insufficient numbers to avoid statistical error. Furthermore, insufficient numbers may permit any of a number of variables such as perioperative infarction, aortic cross clamp time and antecedent history of atrial disease to impact on the results.

The technique of meta-analysis is well-suited to the consideration of these data.[18] By combining information from several studies, it is possible to overcome the limitations of each and to arrive at a meritorious conclusion. In this case, we learned that digitalis (despite its presumed efficacy) may not prevent atrial dysrhythmias after surgery when used alone. This result is in agreement with recent clinical trials that did not find an atrial antiarrhythmic effect in patients with medical atrial fibrillation.[19] Beta blockers do have merit. By preventing excess catecholamine effects in patients (many of whom are withdrawing from β blockers used before surgery), atrial fibrillation was prevented.[20] The combination of the 2 drugs works best, suggesting some synergism when the vagomimetic effects of digitalis are not overridden by catecholamines.[21]

This study has limitations, many of which are generic to meta-analyses.[22] We have no way of considering the many variables that may have contributed to the results of individual studies. Drug selection, dosing and monitoring were all variable. The nonuniformity of design could influence individual results, but hopefully is counterbalanced by the numbers of patients included in the final analyses. The results of the present study should not be used as a final statement, but perhaps can serve as an impetus to initiate a prospective study with enough power to draw strong conclusions that can be used clinically.

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Late (Five to Eight Years) Clinical and Angiographic Assessment of Patients Undergoing Successful Percutaneous Transluminal Coronary Angioplasty

Barry Sharaf, MD, Raymon S. Riley, MD, Thomas M. Drew, MD, and David O. Williams, MD

Little is known concerning the late outcome of patients after successful percutaneous transluminal coronary angioplasty (PTCA). In particular, the angiographic assessment of coronary anatomy late after PTCA is lacking. Accordingly, the purpose of this study was to obtain clinical and angiographic information in a consecutive cohort of patients in whom initial PTCA was successful and in whom ≥5 years had elapsed. Furthermore, we attempted to correlate the angiographic status of the initial PTCA site with clinical status at late follow-up.

Sixty-one consecutive patients who underwent successful PTCA before August 1982 were identified. PTCA was considered successful if the extent of coronary diameter narrowing of the dilated lesion(s) after the procedure was <50% and if the procedure was not complicated by death, myocardial infarction or need for in-hospital coronary bypass grafting surgery. Contact was obtained in 57 of 61 eligible patients (93%) at a mean time of 74 ± 11 months (range 60 to 101) after PTCA. Clinical follow-up status was obtained by telephone interviews with patients, using a standardized questionnaire, and supplemented by review of medical records and by contact with the patients' private physicians.

Angiographic follow-up data were derived from 1 of 2 sources: (1) clinically needed interim angiograms performed at any time during follow-up, and (2) an elective 5-year angiogram in patients who met 1 of the following criteria: (a) no interim angiography performed; (b) interim angiography performed and revealed <50% diameter stenosis at initial PTCA site; (c) interim angiography performed and revealed restenosis of initial PTCA site, and patient was treated with successful repeat PTCA; and (d) interim angiography did not lead to coronary bypass surgery. Accordingly, patients with successful PTCA who demonstrated either recurrent stenosis or new coronary artery disease not amenable to PTCA, and necessitating coronary bypass surgery were considered to have reached their angiographic end point representing unsuccessful PTCA. Therefore, such patients were not restudied at their 5-year anniversary. Before performing elective 5-year angiography, patients and their private physicians were contacted for approval and informed consent.

Angiograms were interpreted visually and by means of calipers for quantification of percent diameter reduction. Death, myocardial infarction and coronary bypass surgery were considered recurrent events. Restenosis was defined angiographically as ≥50% stenosis at the initial PTCA site. Analysis of overall and event-free survival was performed by the Kaplan-Meier method.[1]

Mean age for patients was 53 ± 11 years, and most were men (77%) with 1-vessel coronary disease (82%) involving the proximal or mid-left anterior descending coronary artery (72%). More than 80% of patients were receiving ≥2 antianginal medications at the time of initial PTCA. Prior myocardial infarction was present in 10 patients (18%), and 47 (82%) presented with unstable angina pectoris. Mean diameter reduction of the PTCA site decreased from 71 ± 23% to 26 ± 13%.

Figure 1 depicts survival for the group. There were 3 deaths (2 cardiac and 1 noncardiac). The 2 cardiac deaths were sudden and occurred out of the hospital at 52 and 53 months after PTCA, respectively. At 5 years, survival was 95%.

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Nonfatal myocardial infarctions occurred in 6 patients (11%) at a mean time of 35 ± 17 months (range 12 to 52) after PTCA. Overall, myocardial infarction-free survival at 5 years was 84%.

Coronary bypass surgery was performed in 11 patients (19%) during follow-up at a mean time of 25 ± 25 months after PTCA. Reasons for coronary bypass surgery included angiographically documented restenosis in 8 of 11 patients (73%), and new disease in 3 (27%). At 5 years, 70% of patients were free of a major event, i.e., without coronary bypass surgery, nonfatal myocardial infarction or death.

Repeat PTCA was performed in 15 patients (26%) at a mean time of 30 ± 27 months (range 3 to 72) after initial PTCA. Reasons for repeat PTCA included restenosis in 8 of 15 patients (53%) at a mean time of 14 ± 20 months (range 3 to 60) after initial PTCA, and new disease in 7 patients (47%) at a mean time of 48 ± 23 months (range 36 to 64). Of the 7 patients who had repeat PTCA for a new disease, 7 were successful and were coronary bypass surgery-free at 5 years. Of the 8 patients who had repeat PTCA for restenosis, 5 (63%) underwent coronary bypass surgery.

Cumulative 5-year angiographic information was obtained in 40 of 54 surviving patients (74%). In 12 of these patients (30%) angiography was performed before 5 years and demonstrated restenosis that was not successfully treated with repeat PTCA. For the remaining 28 patients, an elective angiogram was performed at ≥5 years after initial PTCA (mean 68 months, range 61 to 99). Of the 40 patients who had late follow-up angiography, 18 were entirely asymptomatic throughout follow-up. The initial PTCA site was free of significant stenoses in 17 of these patients (94%), although a substantial proportion (7 [39%]) had evidence of new significant disease elsewhere that was clinically silent. Thus, for patients who remained free of recurrent symptoms during follow-up, the finding of angiographic recurrence of stenosis was infrequent. Restenosis was documented angiographically in 12 of 40 patients (30%) at a mean time of 16 ± 24 months after PTCA. Only 3 patients presented with restenosis >1 year after PTCA. Initial therapy for restenosis was repeat PTCA in 8 of 12 patients (75%). In 11 of 12 patients (92%), restenosis was manifested by recurrent angina pectoris. Only 1 patient had silent restenosis that was documented angiographically 12 months after initial PTCA.

The site of the initial PTCA was free of significant stenosis (>50%) in 28 of the 40 patients (70%) with late angiographic follow-up. The extent of diameter reduction before, and immediately and 5 to 8 years after PTCA for these patients is shown in Figure 2. Before PTCA, lesion stenosis was 79 ± 11% and decreased to 29 ± 11% immediately after PTCA. At 5 to 8 years, the degree of stenosis was 21 ± 17%, indicating that for patients who did not develop lesion recurrence there was no attrition in the degree of improvement.

Fourteen of 28 patients (50%) who were free of restenosis had areas of new significant coronary narrowing (>50% diameter reduction) at sites remote from the initial PTCA. These stenoses averaged 76 ± 17% (range 50 to 100). Thus, in a substantial percentage of patients, coronary disease was progressive. Importantly, despite this observation, the initial salutary effects of balloon dilatation at the site of the original lesions were sustained.

In this investigation, successful PTCA provided immediate as well as long-lasting favorable results; after 5 to 8 years of follow-up, 95% of patients were alive, 70% were free of events of death, myocardial infarction or coronary bypass surgery, and 86% reported no symptoms of angina pectoris. These results are particularly significant because most patients initially presented with unstable angina pectoris, and the techniques of PTCA were less refined when these patients were treated than at present.

Only 2 cardiac deaths occurred in this study group over a total period of 4,107 patient months of follow-up. This favorable survival rate is comparable to that of previous reports of patients undergoing PTCA.[2-8]

The myocardial infarction-free rate of 89% reported herein is slightly lower than noted in other studies.[2,4-8] As reported by Talley et al,[8] freedom from myocardial infarction status during a period of 60 months was 94%. Furthermore, in our report, 5 of the 6 myocardial infarctions were related to disease of arteries remote from the

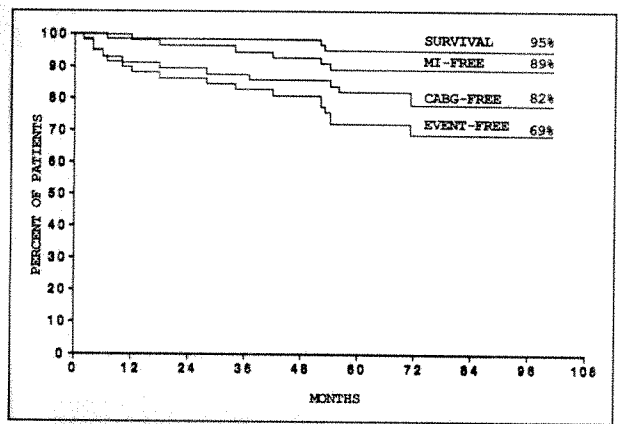


FIGURE 1. Five-year cumulative survival and event-free rates for 57 patients after successful coronary angioplasty. Event-free includes patients who are alive and did not have either myocardial infarction (MI) or coronary artery bypass graft surgery (CABG).

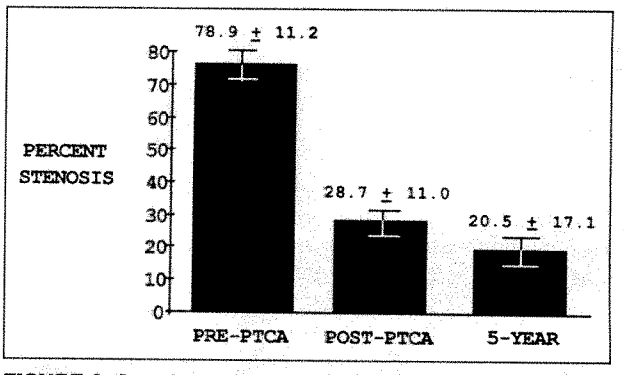


FIGURE 2. Severity of coronary stenosis before, and immediately and 5 years after successful percutaneous transluminal coronary angioplasty (PTCA) in the 28 patients who remained free of coronary bypass surgery. Values indicate mean ± 1 SD.

initial site of PTCA and thus represented a manifestation of the natural history of coronary disease, rather than an unsuccessful PTCA. In fact, nonfatal myocardial infarction was never attributed to restenosis. These observations are consonant with other reports suggesting that myocardial infarction is an infrequent manifestation of restenosis.

Coronary bypass surgery was ultimately needed in 19% of patients. In most cases, the indication for coronary bypass surgery was restenosis of the initial PTCA lesion. Hence, once initially successful PTCA is achieved, the ability to perform subsequent elective coronary bypass surgery is not compromised. It is possible that with new device development, surgery may have been obviated in many of these patients.

Repeat PTCA was performed in 15 patients with indications equally divided between lesion recurrence and the development of new disease. In each case where PTCA was performed for new disease, the procedure was successful and provided sustained clinical improvement, as each of these patients remained free of coronary bypass surgery throughout follow-up. PTCA in these patients represents a treatment strategy that can be applied serially and successfully over the course of a disease that by nature tends to be progressive. In contrast, most patients who underwent PTCA for restenosis had recurrent symptoms and subsequently needed coronary bypass surgery. This finding is in agreement with the early Zurich experience in which 19 of 27 patients who underwent repeat PTCA for restenosis subsequently needed coronary bypass surgery.[3] Such observations support the concept that patient-based factors influence responsiveness to PTCA and may predict patients at risk for recurrent restenosis.

The angiographic restenosis rate of 30% noted in this report is similar to that of many series.[2-8,9-11] The restenosis rate in our study is potentially higher than actual, because patients who returned for angiographic follow-up were more likely to be symptomatic than those who refused.

Follow-up angiography confirmed the durability of PTCA. Seventy percent of study patients had sustained anatomic improvement at the site of the initial PTCA. This value may actually underestimate the true proportion of patients achieving a sustained favorable angiographic outcome, because all those who refused angiographic follow-up were asymptomatic.

Angiography did not demonstrate any evidence of attrition in the magnitude of diameter reduction initially achieved by PTCA among patients who remained free of restenosis. This observation was noted previously in a series with a smaller number of patients with late angiographic follow-up.[4] In fact, a trend toward mild improvement in percent stenosis of the PTCA site was observed despite progression of disease of other coronary arterial sites in many patients. Thus, in patients who do not present with early restenosis PTCA may have a protective effect against atherosclerotic progression.

This investigation indicates that PTCA can provide long-term favorable clinical and angiographic results for selected patients with coronary disease. PTCA is of particular value for those patients who do not develop restenosis after an initial procedure, because continued benefit can be anticipated from repeat PTCA should other lesions occur. For those patients who develop restenosis and are eventually treated surgically, PTCA may be of value in delaying coronary bypass surgery, a more complex procedure with a finite life of its own.

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Effectiveness of Percutaneous Transluminal Coronary Angioplasty in Cardiogenic Shock During Acute Myocardial Infarction

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The prognosis of cardiogenic shock during acute myocardial infarction (AMI) is poor; the mortality rate varies from 80 to 100%.[1,2] Recently, interventional therapy including intracoronary thrombolysis and mechanical recanalization have been proposed and seem to improve prognosis.[3-5]

Since 1983, we have treated 21 patients presenting with cardiogenic shock during AMI by emergency percutaneous transluminal coronary angioplasty. The results are reported here. Hospital charts were reviewed. Seventeen men and 4 women, mean age 62 ± 11 years, were studied. A history of previous AMI was present in 6 patients (29%) and 5 patients (23%) had angina pectoris. Coronary angiography was performed in all patients and showed occlusion of at least 1 coronary vessel. The clinical and angiographic characteristics are summarized in Table I. The mean delay between chest pain and the onset of cardiogenic shock was 135 minutes (range 60 to 210). The mean delay between the onset of shock and mechanical recanalization attempts was 16 ± 21 hours. One-vessel disease was present in 6 patients, and multivessel disease in 15 (narrowing >50%). Furthermore, 2 patients had a left main coronary occlusion.

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TABLE I Clinical, Hemodynamic and Angiographic Data of the 21 Patients

	All Patients	Survivors	Nonsurvivors
No. of pts.	21 (100%)	12 (57%)	9 (43%)
Men/women	17/4	9/3	8/1
Age (years, mean ± SD)	62 ± 11	60 ± 12	64 ± 10
Previous infarction	6	2	4
Treated angina	5	3	2
Localization of the present infarction			
Anterior	13	7	6
Inferior	6	3	3
Undetermined	2	2	—
Number of coronary arteries narrowed >50% in diameter			
1	6	2	4
2	6	5	1
3	9	5	4
Successful recanalization	18	12	6
Delay between onset of shock and recanalization (hours)	16 ± 21	21 ± 25	11 ± 15
Systolic blood pressure on admission in the cath. lab. (mm Hg)	83	83 ± 19	82 ± 21
Heart rate (beats/min)		85 ± 30	82 ± 28

cath. lab. = catheterization laboratory.

Cardiogenic shock was defined as prolonged systolic blood pressure of <80 mm Hg without inotropic support, and signs of cutaneous or cerebral hypoperfusion or oliguria. (<30 ml/hour), or a combination. In patients with hemodynamic monitoring (Swan-Ganz catheter) shock was defined as cardiac index <2.0 liters/min/m^2, pulmonary artery occlusion pressure >12 mm Hg, and absence of response to volume expansion.

AMI was defined as prolonged chest pain consistent with myocardial ischemia, ST-segment elevation of ≥0.2 mV in limb or precordial leads and creatine kinase-MB enzyme elevation.

Recanalization was considered successful if visual estimation of the residual stenosis was <50%.

Mechanical recanalization was performed immediately after conventional coronary angiography. An 8Fr introducer was placed in the right or left femoral artery. Right and left coronary angiography was performed using a Judkins or Amplatz catheter. After visualization of the occluded vessel, a guiding catheter was positioned in the coronary ostium. Intracoronary infusion of urokinase was begun (2,000 to 4,000 U/min) and a bolus dose of heparin (15,000 IU) was administered intravenously. A 0.014-inch soft wire was advanced through the occlusion and percutaneous angioplasty was performed. Inflations were repeated until obtaining a residual stenosis of <50%. The urokinase infusion was then continued for 1 to 3 hours and heparin was infused for 24 hours with a target partial thromboplastin time of >60 seconds. Angioplasty of other vessels than the infarct-related one was attempted when considered useful by the operator. Stenoses of >50% were dilated whenever possible according to the angiographic morphology of the stenosis. Before recanalization, 5 patients had to be resuscitated, 9 were mechanically ventilated and 4 needed intraaortic balloon counterpulsation, using the percutaneous technique. A Swan-Ganz catheter was placed in 9 patients before angioplasty. The results are expressed as mean ± 1 standard deviation. Tests for differences between the means were performed with a 2-tailed Student's t test. A p value <0.05 was considered statistically significant.

Successful recanalization was achieved in 18 patients (85%). Nine patients (43%), 6 of whom had had successfully recanalization, died 1 to 3 days after coronary angioplasty. There was no difference between the survivors and nonsurvivors regarding age, localization of the infarction, number of diseased vessels, delay between onset of chest pain and occurrence of shock. The mean delay between the onset of cardiogenic shock and recanalization was significantly shorter in the nonsurvivors than in the survivors (11 ± 15 hours vs 21 ± 25 hours) (p <0.05). The mean creatine kinase value was not different between survivors and nonsurvivors (3,450 ± 320 IU/liter vs 4,150 ± 130 IU/liter). Mean echocardio-

graphic ejection fraction after angioplasty was 35 ± 8% in the survivors group. In 5 patients, a second angioplasty was performed during the same procedure on a vessel different from the infarct-related one. Three of them survived. Hemodynamic data were obtained before angioplasty in 9 patients and after intervention in 10. All patients were receiving inotropic support (combination of dobutamine and dopamine occasionally associated with noradrenaline). Rapid and marked hemodynamic improvement occurred in all survivors (Table II). Ventricular arrhythmia developed in 17 patients and needed electrical cardioversion in 8. Two patients with successful left main recanalization underwent coronary artery surgery immediately after the procedure.

TABLE II Hemodynamic Data

	Baseline	After Angioplasty	Before Leaving Intensive Care
Survivors (n = 8)			
CI (liters × min^{-1} × m^{-2})	2 ± 0.5	2.7 ± 0.6*	3.5 ± 0.7*
SI (ml × min^{-1} × m^{-2})	19 ± 6	31 ± 9*	39 ± 7*
PA occlusion pressure (mm Hg)	22 ± 7	16 ± 6*	14 ± 5*
HR (beats/min)	101 ± 15	101 ± 15 (NS)	100 ± 15 (NS)
SBP (mm Hg)	97 ± 7	104 ± 16 (NS)	109 ± 10 (NS)

*$p < 0.05$.
CI = cardiac index; HR = heart rate; NS = not significant; PA = pulmonary artery; SBP = systolic blood pressure; SI = systolic index.

In patients treated medically in the setting of AMI complicated by cardiogenic shock, mortality remains very high (up to 80 to 90%). At the present time the aim of therapy is to restore an effective coronary blood flow by using different techniques. Successful coronary reperfusion achieved with percutaneous transluminal coronary angioplasty of the infarct-related vessel improves prognosis by reducing mortality to approximately 50%, as shown by Meyer[4] and Lee[5] and their co-workers. Our results with a 57% survival rate confirm these data. Circulatory assistance with percutaneous intraaortic balloon counterpulsation was needed before performing angioplasty in only 4 patients in our series. Systematic use of percutaneous cardiopulmonary bypass before performing coronary angioplasty was proposed by Shawl et al in 1989. A major drawback of this technique consists in the size of the cannula which precludes its use in patients with iliofemoral disease. Before its widespread use can be recommended, its superiority to intraaortic balloon counterpulsation needs to be demonstrated. Other investigators have reported better results after surgical revascularization with intraaortic counterpulsation in patients with cardiogenic shock associated with AMI. The advantage of percutaneous transluminal coronary angioplasty is to allow an immediate restoration of coronary flow and hence shorten the ischemic time, with a possible limitation of necrosis. The proportion of successful recanalizations in our series of patients with cardiogenic shock is very similar to that reported for AMI without shock.[6,7] Multivessel disease was present in most of our 15 patients. More than 1 angioplasty was performed in 5 patients, 3 of whom rapidly improved and finally survived. It seems therefore that angioplasty should not be strictly reserved for patients with 1-vessel disease. This procedure, which has been shown to be safe when achieved electively, might be applied with success to emergency situations as suggested by our preliminary results.

The dramatic hemodynamic improvement documented in some of our patients demonstrates the beneficial effect of reperfusion on left ventricular function. The hemodynamic response was either rapid and immediate (7 patients) or progressive over a period of 24 to 36 hours (5 patients).

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INDICATIONS AND USAGE
Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris
Lopressor is indicated in the long-term treatment of angina pectoris.

Myocardial Infarction
Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).

Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.25 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Risk of Anaphylactic Reaction. While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practelol has not been reported with Lopressor.

Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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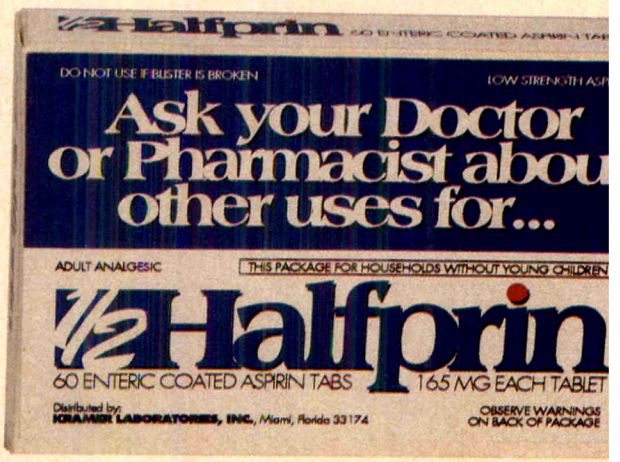
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Long-Term Amiodarone Therapy and Antithyroid Antibodies

Hilário Bastos Machado, MD, Maria Emília Pereira da Silva, MD, and Bernardino Pinho, MD

Amiodarone is a benzofuran antiarrhythmic drug widely used in Europe and South America, and also approved for use for ventricular arrhythmias in the United States. Each amiodarone tablet (200 mg) contains 75 mg of iodine, which can induce hyperthyroidism and, more frequently, hypothyroidism in long-term therapy; this requires periodic monitoring of thyroid function in order to detect subclinical disorders. It has been suggested that an additional mechanism of thyroid disease could be immunologic disorders induced by the amiodarone itself[1,2]; the presence of antithyroid antibodies are even an early marker for thyroid disease,[1] but this has not been been confirmed by other studies[3,4] using different antibody detection methods. To clarify the different results, we prospectively studied the presence of antithyroid antibodies in patients before and during long-term administration of amiodarone, both by indirect immunofluorescence (used in the studies in which a high percentage of positive cases was detected) and by immunohemagglutination methods.

Amiodarone was administered in uniform doses of 1 g/week (without an initial loading dose) to 179 patients (75 men and 104 women) with reentrant supraventricular tachycardias. The mean patient age was 50 ± 14 years; they had neither congestive heart failure, significant coronary heart disease nor clinical past or present thyroid disease. In 61 patients thyroid function and antithyroid antibodies were determined before amiodarone therapy was begun and within months intervals. Concentrations of triiodotironine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) were determined by radioimmunoassay (RIA); antithyroid (thyroglobulin and microsomal) antibodies were detected by immunofluorescence and immunohemagglutination (Thymune M and Thymune T, Wellcome, Dartford, England) methods without knowledge of whether patients were or were not receiving amiodarone therapy. The administration of amiodarone was discontinued in those with abnormal thyroid function; in patients with positive detection of antithyroid antibodies by the immunofluorescence method, determination was repeated and amiodarone therapy discontinued only in patients with positive detection also by the immunohemagglutination method.

In 179 patients, there were 417 determinations of thyroid function and antithyroid antibodies. In 53 patients (cumulative percentage 30%), the amiodarone therapy was stopped because of abnormal levels of T4, T3 or TSH (subclinical hypo- or hyperthyroidism), but only 2 patients developed clinical hypothyroidism; no patient developed clinical hyperthyroidism or euthyroid goiter. In patients with hypothyroid and in those with subclinical disorders, no specific treatment was given, and the return to normal levels and clinical signals remained constant at 6-month control after amiodarone withdrawal. Fluctuation in the levels of T4 and T3 were seen in some patient; an abnormal high level of TSH remained when amiodarone was not withdrawn. One hundred sixty-eight determinations of antithyroid antibodies were by the immunofluorescence and 249 were by the hemagglutination method. The results are summarized in Table I. Thirty-three percent of patients had positive antithyroid antibodies before amiodarone therapy (control) by the immunofluorescence detection method, and only 0.03% of patients had positive antibodies by the hemagglutination detection method; striking differences were also seen with amiodarone therapy.

Follow-up of patients with positive antithyroid antibodies by the immunofluorescence detection method without amiodarone withdrawal showed that, 27% of the patients continued to have a positive detection, 64% had subsequent negative detection, and 9.0% had flutuations in the positivity. Only 1 patient had positive detection by both methods (amiodarone therapy discontinued). This patient also had an elevated level of TSH. In the 2 patients with clinical hypothyroidism, 1 had negative antithyroid antibodies (immunohemagglutination) and the other had a positive followed by a negative detection 3 months later (immunofluorescence).

A high-level iodine supplement intake can produce thyroid function disorders. With uniform low-dose amiodarone therapy, 1,000 mg/week, the release of approximately 30 mg of free iodine into the blood stream in this period of time is anticipated. During long-term therapy, as in the present study (6 to 120 months) it is well known that thyroid function disorders can occur (cumulative percentage of 30% in our patients) requiring periodic determinations of T4, T3 and TSH levels.

The question of whether iodine released by amiodarone or amiodarone itself could trigger the development of thyroid autoimmunity, thus causing thyroid function disorders, is still controversial. An imbalance of T-cell subpopulations was observed in 2 of 10 patients with

TABLE I Antithyroid Antibodies in Control and Long-Term Amiodarone Therapy (60 to 120 months) Detected by Immunofluorescence Versus Hemagglutination Methods (417 determinations)

Follow-Up (mos)	Immunofluorescence			Hemagglutination		
	No.	ATA+	%	No.	ATA+	%
0 (control)	27	9	33	34	1	0.03
6–12	24	12	50	26	0	0
12–24	67	19	28	62	0	0
24–48	41	4	10	63	1	0.02
48–120	9	3	33	64	1	0.02

ATA+ = positive detection of antithyroid antibodies.

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thyroid disorders, receiving amiodarone therapy,[2] and also in other patients with underlying cardiac diseases who did not take amiodarone.[5] A close relation between amiodarone intake and the presence of antithyroid antibodies[1,2] has not been confirmed by other studies,[3,4] the discrepancy being attributed to different amounts of iodine intake in different geographical areas. The population of the present study was referred to an arrhythmology clinic without other significant underlying cardiac diseases, and because both techniques of antibody detection were applied, there were no different geographical areas. The immunofluorescence detection technique was used in the studies showing a close relation between amiodarone intake and antithyroid antibodies.[1,2] The possibility of a high percentage of false-positive results by this method can be explained in part by the use of thyroid sections: the assay of microsomal antibodies were complicated by the thyroglobulin that microsomal antigen preparations inevitably contain; this can subsequently interact with antibodies directed against thyroglobulin rather than microsomal antigen, giving false-positive results.[6] A poor reproducibility on the borderline level (weak positive) can be one other potential source of error. The follow-up of patients with positive determinations of antibodies by the immunofluorescence detection method, in whom amiodarone therapy was continued, showed no clinical significance. Amiodarone was discontinued only in 1 patient with persistent positive antibodies by both the immunofluorescence and hemagglutination methods, and this patient also had abnormal TSH levels.

In conclusion, it is recommended that with low-dose, long-term amiodarone therapy, periodic determinations of thyroid and thyrostimulin hormones be conducted in order to detect subclinical thyroid disorders. This study found no relation between amiodarone and the presence of antithyroid antibodies; a positive relation suggested detection methodologic artifact.

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Idiopathic "Dilated" Cardiomyopathy With or Without Mild Dilatation of the Cardiac Ventricles in Multiple Family Members

Edgardo Zimmerman, MD, Abraham Chwojnik, MD, and Jorge Lerman, MD

Idiopathic dilated cardiomyopathy (IDC) is characterized by cardiac dilatation, with a left ventricular (LV) diastolic diameter generally measuring ≥65 mm[1] associated with impaired LV function and an LV ejection fraction usually <40%.[2] The presence of a markedly reduced LV function with only minimally dilated or nondilated ventricles is unusual. This condition was first described by Keren et al.[3] It has been suggested that IDC can be familiarly aggregated in about 6% of cases.[4] In this report, we present a family with IDC in whom multiple members had significantly reduced ventricular function, but only minimally enlarged or not enlarged chambers.

Figure 1 depicts the pedigree of the family, consisting of the parents, 5 sons and 2 daughters. The father, who had had clinical manifestations of congestive heart failure for 3 years, was admitted to the hospital with pulmonary edema and died 1 week later. The eldest son was admitted to the hospital with congestive heart failure (functional class IV), successfully treated and discharged. In both cases, the workup study suggested the diagnosis of IDC. Other family members were asymptomatic and had no evidence of heart disease on physical examination. The mother, 2 daughters and youngest son had normal studies. The other 3 sons had reduced ventricular systolic function manifested by low LV fractional shortening on echocardiogram or by a low ejection fraction on radionuclide study and were considered to have IDC. In the 2 symptomatic and 1 asymptomatic patient (the one with the lowest fractional shortening), cardiac catheterization was performed. All subjects were followed up for 3 years. The symptomatic son remained in functional class III–IV and overcame 2 additional admissions to the hospital for pulmonary edema, and cardiac transplantation was indicated. The remaining

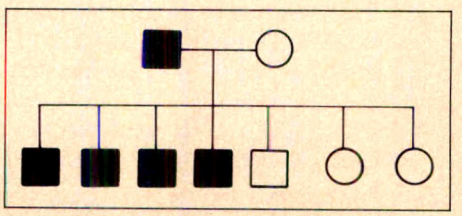


FIGURE 1. Pedigree of family. *Circles:* women; *squares:* men; *black symbols:* affected subjects; and *open symbols:* nonaffected subjects.

From the Servicio de Cardiologia, Hospital Interzonal de Agudos Evita, Lanus, Provincia de Buenos Aires, and the Division Cardiologia, Hospital de Clinicas Jose de San Martin, Universidad de Buenos Aires, Buenos Aires, Argentina. Dr. Zimmerman's address is: Av Santa Fe 2966, Piso 2, Dep C, Buenos Aires (1425), Argentina.

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TABLE I Clinical Findings and Results of Echocardiography, Radionuclide Studies and Cardiac Catheterization in Five Patients with Idiopathic "Dilated" Cardiomyopathy

				Echocardiography						Radionuclide		
Pt.	Age (yr)	CHF	BS (m^2)	LVDD (mm)	LVSD (mm)	FS (%)	RVD (mm)	LAD (mm)	M–S (mm)	LVEF (%)	RVEF (%)	EMB
1	58	+	1.9	66	60	9	18	40	28	21	16	*
2	34	+	1.9	56	43	23	14	44	25	29	25	*
				(64)	(54)	(16)	(16)	(43)	(28)	(20)	(22)	
3	23	0	2.1	57	43	24	18	43	17	43	26	*
				(61)	(46)	(23)	(17)	(43)	(18)	(45)	(25)	
4	30	0	2.0	63	45	29	13	41	15	43†	28†	—
				(60)	(40)	(28)	(14)	(44)	(17)			
5	27	0	1.8	49	32	35	12	40	10	39	34	—
				(50)	(32)	(36)	(12)	(39)	(8)	(38)	(32)	

*Myocytolisis, lymphocytic infiltrates, intracellular and interstitial edema, and interstitial fibrosis.
†Refused to undergo second radionuclide study.
Numbers in parentheses are results of study obtained 30 to 36 months later.
BS = body surface; CHF = congestive heart failure; EMB = endomyocardial biopsy; FS = fractional shortening; LAD = left atrial dimension; LVDD = left ventricular diastolic dimension; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dimension; M–S = mitral valve–septal distance; RVD = right ventricular dimension; RVEF = right ventricular ejection fraction.

subjects maintained their asymptomatic status. Echocardiographic and radionuclide studies were obtained in the 4 surviving subjects every 6 to 8 months during follow-up.

Table I summarizes data obtained by echocardiography, radionuclide angiocardiography and cardiac catheterization in the 5 patients considered to have IDC. Case 1 presented typical IDC with severe congestive heart failure, ventricular dilatation and reduced ventricular function. Case 2 had end-stage congestive heart failure and markedly reduced ventricular function, but normal-sized ventricles at initial examination (Figure 2). Cases 3 and 5 were young asymptomatic subjects with nondilated ventricles, but impaired systolic ventricular function. Case 4 had both dilatation and reduced systolic ventricular function. Comparison between the initial noninvasive study and that obtained 30 to 36 months later demonstrated a trend toward mild dilatation and deterioration of systolic function in most patients. Cardiac catheterization showed similar findings in the 3 patients in whom the procedure was performed. Left ventriculography demonstrated diffuse hypokinesis (more severe in cases 1 and 2). Coronary arteries were normal. Endomyocardial biopsy showed lymphocytic infiltrates, interstitial fibrosis, intracellular and interstitial edema, and patches of myocytolysis. In case 1, thrombotic material was found adhered to the endocardial surface.

Twenty cases have been reported with mildly dilated IDC to date.[5] This condition represents 5% of patients with IDC undergoing heart transplantation at Stanford University.[5] The present report represents the first study in which an entire family with cases of mildly or no dilated IDC is studied and followed-up. Most cases presented in previous series were women.[5] Conversely, all our patients were men.

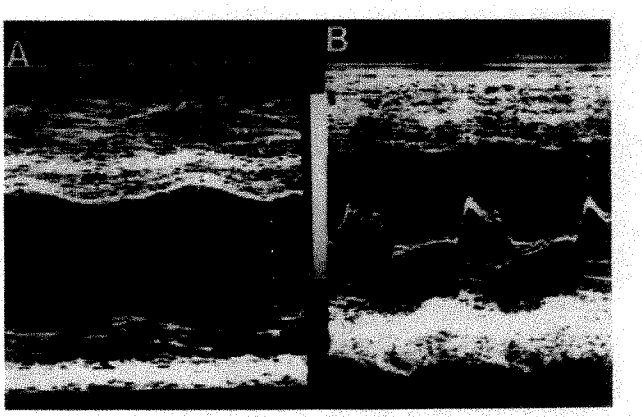


FIGURE 2. Case 2. *A*, M-mode echocardiogram that shows mildly dilated left ventricle and markedly reduced systolic ventricular function. *B*, M-mode echocardiogram of mitral valve showing increased distance between interventricular septum and anterior mitral leaflet.

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Noninvasive Differentiation of Noncoronary from Coronary Cardiomyopathy

Diaz and distinguished collaborators[1] have established what many of us had long suspected: In a population of patients with chronic heart failure, 2-dimensional echocardiography combined with Doppler and color flow imaging failed to differentiate patients with dilated cardiomyopathy from those with coronary disease. In pointing out an alternative approach, I wish to supplement their observations rather than to contest them.

Noninvasive differentiation between dilated cardiomyopathy and coronary disease with myocardial failure is indeed possible utilizing cardiographics ("mechanocardiography"), more or less disused, but accurate and inexpensive methods (viz., systolic time intervals and central pulse transmission time). We reported on 11 patients with dilated cardiomyopathy and on 11 age- and sex-matched patients with coronary artery disease.[2] There were significant differences in central pulse transmission time (time from the aortic component of the second heart sound to the carotid incisura) and preejection period (both $p < 0.001$), ejection time index ($p < 0.05$) and ratio of preejection period to left ventricular ejection time ($p < 0.001$). All systolic interval indexes were markedly more abnormal in the cardiomyopathy group, and pulse transmission time averaged 50% longer than in the coronary artery patients. At the time of publication this was not surprising, because comparable figures for a larger series of patients with alcoholic cardiomyopathy compared with those for 2 sets of matched control subjects had shown comparable trends.[3] Incidentally, systolic intervals can be determined from the M-mode echogram.

Finally, why title an article, "Usefulness . . .," when the results indicate that the more accurate title would begin, "Futility . . ."?

David H. Spodick, MD, DSc
Worcester, Massachusetts

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Diastolic Ventricular Function After the Fontan Operation

We recently read the article concerning ventricular diastolic function in patients after the Fontan operation by Frommelt and co-workers.[1] We,[2] like Frommelt, have also observed a reduction in early diastolic filling velocity in these patients. Our data, however, may provide further insights into the mechanisms responsible for these filling abnormalities.

The hypothesis that the reduction in early diastolic filling may be a reflection of ventricular dilatation and reduced contractility cannot be supported. To the contrary, our data and those of other investigators[3,4] suggest that the transition to a Fontan circulation is associated with a reduction in ventricular cavity size and a well-maintained systolic function.

The second hypothesis,[1,2] that the reduction in early diastolic filling may be a reflection of impaired ventricular relaxation, appears more plausible. We[2] have looked at ventricular relaxation in these patients in some detail and have demonstrated that isovolumic relaxation time is significantly longer and early diastolic filling velocity is lower in patients after the Fontan operation, compared with age- and sex-matched control subjects and compared to children with a univentricular atrioventricular connection, before the Fontan operation. Our observation of a significant inverse correlation between isovolumic relaxation time and early diastolic filling velocity underscores the close relation between ventricular relaxation and filling in these patients (Figure 1). We[3] have also shown a prolongation in time constant of ventricular relaxation, early after the Fontan operation.

Although not explored by the authors,[1] a careful analysis of Figure 1 and particularly Figure 2 from Frommelt's paper may provide an important clue as to the possible mechanisms responsible for this impaired ventricular relaxation. The demonstration of intracavitary flow in these patients during ventricular relaxation must not be overlooked. We have previously highlighted the prevalence of intracavitary flow in

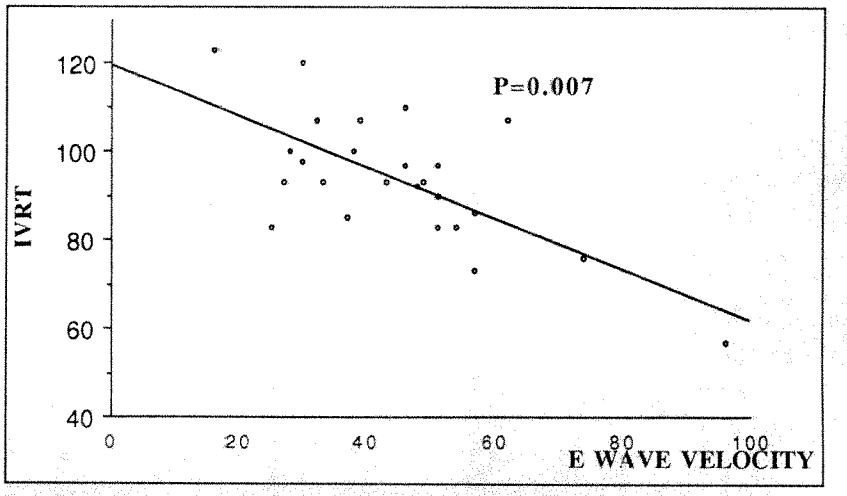


FIGURE 1. Plot of early diastolic filling velocity (E WAVE VELOCITY) against isovolumic relaxation time (IVRT) in 25 patients after the Fontan operation, demonstrating a close, inverse relation.

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patients after the Fontan operation[2] and have postulated that as in others,[5] this flow may reflect the development of incoordinate ventricular relaxation. Frame-by-frame digital analysis of ventricular angiograms have provided further weight to our hypothesis.[6]

We wonder whether Frommelt et al have any further information regarding ventricular relaxation in this fascinating patient group.

Daniel J. Penny, MB, MRCP
Andrew N. Redington, MD
London, United Kingdom
12 November 1991

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6. Penny DJ, Redington AN. Angiographic demonstration of incoordinate motion of the ventricular wall after the Fontan operation. *Br Heart J* 1991;66: 456–459.

REPLY: We agree with Penny and Redington that ventricular filling dynamics, including ventricular relaxation, play a major role in determining the pattern of pulmonary artery flow following Fontan. We also found that changes in the mitral inflow Doppler were consistent with abnormalities in ventricular relaxation and a decreased early diastolic transvalvular pressure gradient when compared with normal subjects. This resulted in decreased early diastolic transvalvular flow and a delay in diastolic forward pulmonary artery flow.

Penny correctly points out that with the transition to a Fontan circulation, most patients have a reduction in ventricular size with well-preserved systolic function. We identified a subset of Fontan patients, however, who had depressed ventricular contractility and persistently increased end-diastolic and end-systolic ventricular dimensions. It was in this group of patients that *systolic* pulmonary artery flow was significantly decreased, suggesting an abnormality in mitral valve excursion/suction effect during ventricular contraction with a resultant increase in systolic atrial filling pressures. Diastolic pulmonary artery flow also shifted to late diastole in these patients, suggesting a deterioration in diastolic ventricular function as well.

The idea of intracavitary diastolic flow gradients is interesting. Although we have not explored this, per se, we have observed a mid-diastolic increase in transmitral flow between the E and A waves in many Fontan patients. This may be related to "incoordinate" ventricular relaxation with the development of mid-diastolic pressure gradients as different parts of the ventricle relax in a nonuniform fashion.

Peter C. Frommelt, MD
Milwaukee, Wisconsin
16 January 1992

Effects of Captopril on Infarct Expansion

I would like to comment about the report on the use of early captopril administration in patients with acute myocardial infarction (AMI) by Oldroyd et al.[1] The presence of an excess number of patients with previous AMI in the placebo group might have influenced the outcome of the study, although the baseline left ventricular ejection fractions were said to be well-matched. Matching in this respect would have helped in drawing more definite conclusions from the study. Another point is the use of placebo in 1 group of patients, when β blockers have already emerged as promising secondary prevention agents in the case of AMI, capable of influencing the outcome favorably. Placebo-controlled trials were severely criticized previously, especially when an effective alternate therapy already exists.[2] The aim of clinical research should be to compare the new treatment with the best available current therapy. Moreover, β blockers could also lead to reduction of the wall stress, and this might be one contributing factor in reducing long-term mortality in patients given β blockers in early intervention (within 72 hours of AMI) protocols. The possible effect of captopril on the precapillary sphincter and consequently on the total ischemic burden were also not touched on in the article.

I would also like to comment on the "informed written consent" given by the patients before entry. In a case like AMI, with the pain, stress, effects of medications, and so forth, is it ethical to add the burden of decision making regarding participation in a clinical trial to the patient? And what effect will it have on the outcome of such a study?

P. Dileep Kumar, MD
Calicut, Kerala, South India
10 December 1991

1. Oldroyd KG, Pye MP, Ray SG, Christie J, Ford I, Cobbe SM, Dargie HJ. Effects of early captopril administration on infarct expansion, left ventricular remodeling and exercise capacity after acute myocardial infarction. *Am J Cardiol* 1991;68:713–718.
2. Hait WN. Ondansetron and cisplatin induced nausea and vomiting. *N Engl J Med* 1990;323:1485–1486.

REPLY: In reply to the letter from Dr. Kumar, I offer the following comments. We certainly consider that the excess number of patients with previous AMI in the placebo group might have influenced the outcome of the study and accordingly performed an additional analysis after excluding these patients. As indicated in the manuscript, this analysis confirmed the findings shown when all patients were analyzed together. There was no restriction on the use of β blockade in this study, and the numbers of patients receiving β blockers in the placebo and captopril groups were similar. We did not address the question of "total ischemic burden" in these patients, but were certainly not able to show any effect of captopril on exercise-induced ischemia in these postinfarct patients.

I find the comment on "informed written consent" rather difficult to understand. Tens of thousands of patients with acute myocardial infarction have been randomized in double-blind placebo-controlled studies. Without such studies we would not have the large data of incontrovertible evidence supporting the use of thrombolytic therapy early in myocardial infarction. Although discussing the pros and cons of entry into a clinical study with a patient who has recently had a myocardial infarction might prove stressful, I would certainly prefer it to entering these patients into such trials without their consent.

Keith G. Oldroyd, MRCP
Glasgow, Scotland
13 January 1992

Mechanism of Concealed Bigeminy

We read with much interest the article by Nilsson et al[1] on ventricular premature complexes in which they explained the mechanism of concealed bigeminy on the theory of "modulated parasystole." We believe that in most clinical cases of ventricular concealed bigeminy, ventricular premature complexes originate not in a parasystolic focus but in a reentrant pathway. We would like to suggest an alternative explanation by use of the concept of "2:1 concealed reentry."[2]

We originally reported on the phenomena of "concealed bigeminy and trigeminy" in 1960,[3] before the report by Schamroth and Marriott.[4] The accompanying figure shows an example of concealed bigeminy. The first 4 strips are continuous. The numbers of sinus QRS complexes (S) intervening between 2 successive manifest premature complexes (X) are all uneven. Time intervals are expressed in hundredths of a second. Coupling intervals of premature complexes to the preceding sinus QRS complexes are represented by *numerals within parentheses*, which are markedly variable. In the *bottom strip*, an SS interval is markedly prolonged (2.80 seconds), because of temporary sinus arrest caused by vagal stimulation; however, no ectopic QRS complexes are found in the SS interval. The period of 2.80 seconds is much longer than the sum of the XS_1X (1.53 seconds) and shortest coupling (0.48 second) intervals. These findings indicate that premature complexes in this case do not originate in a parasystolic focus, because it is known that vagal stimulation hardly suppresses parasystolic impulse formation.

The *diagram below the third strip* shows that concealed bigeminy is caused by 2:1 concealed reentry.[2] In the diagram, *shaded bars* represent abnormally long effective refractory periods in a reentrant pathway (RP). A concealed reentrant extrasystole (X) and 2:1 block of sinus impulses in the reentrant pathway are shown. V represents the ventricles. The findings in this case strongly suggest that concealed bigeminy is usually caused not by modulated parasystole, but by 2:1 concealed reentry.

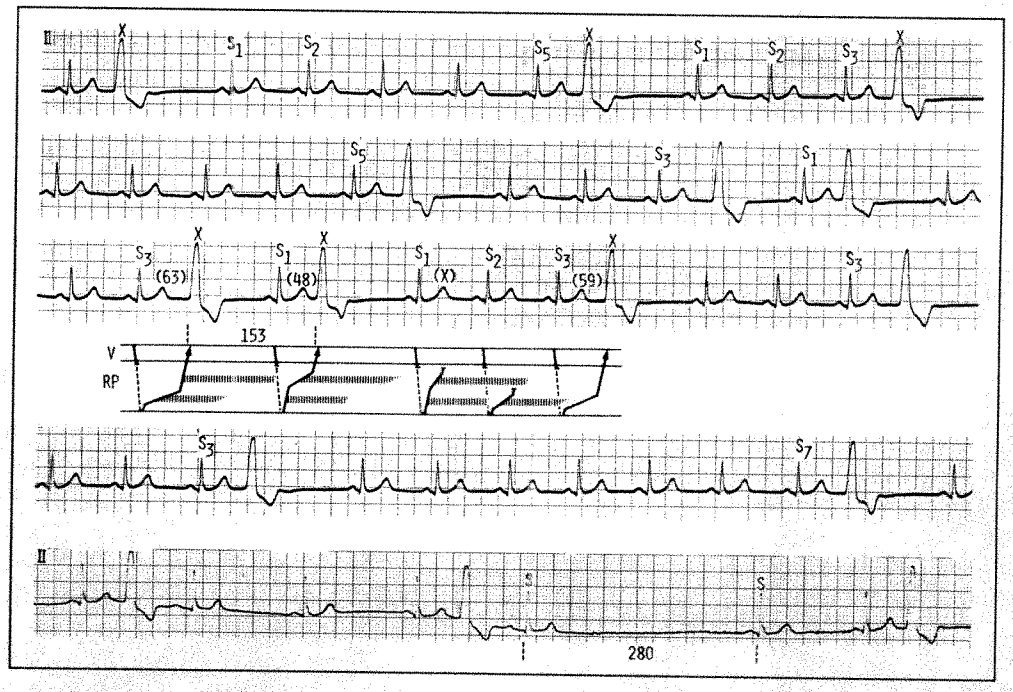
Shinji Kinoshita, MD
Fumihiko Okada, MD
Sapporo, Japan
20 November 1991

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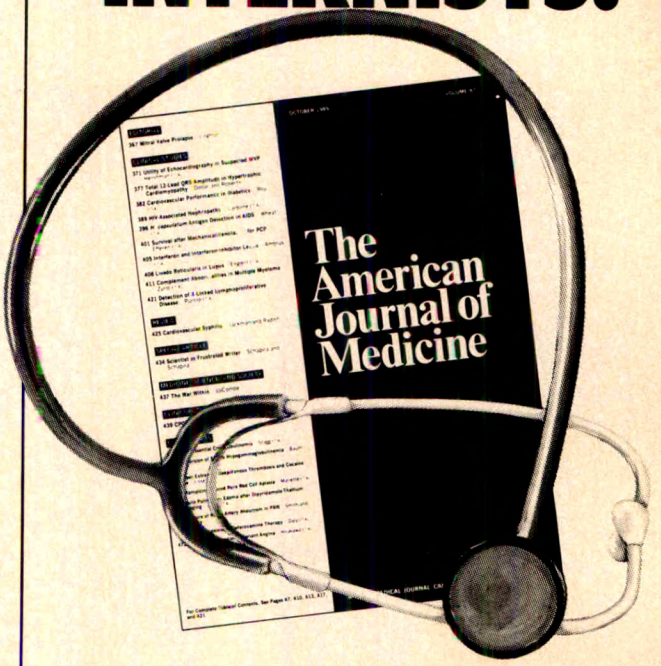
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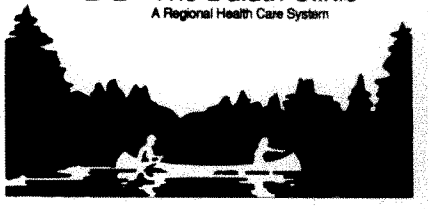
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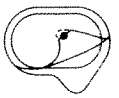
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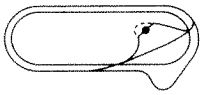
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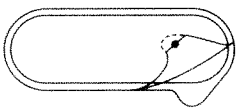
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Transderm-Nitro®
nitroglycerin

Transdermal Therapeutic System

Revised Dosage Information

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
This drug product has been conditionally approved by the FDA for the prevention of angina pectoris due to coronary artery disease. Tolerance to the antianginal effects of nitrates (measured by exercise stress testing) has been shown to be a major factor limiting efficacy when transdermal nitrates are used continuously for longer than 12 hours each day. The development of tolerance can be altered (prevented or attenuated) by use of a noncontinuous (intermittent) dosing schedule with a nitrate-free interval of 10-12 hours.

Controlled clinical trial data suggest that the intermittent use of nitrates is associated with decreased exercise tolerance, in comparison to placebo, during the last part of the nitrate-free interval; the clinical relevance of this observation is unknown, but the possibility of increased frequency or severity of angina during the nitrate-free interval should be considered. Further investigations of the tolerance phenomenon and best regimen are ongoing. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS
Allergic reactions to organic nitrates are extremely rare, but they do occur. Nitroglycerin is contraindicated in patients who are allergic to it. Allergy to the adhesives used in nitroglycerin patches has also been reported, and it similarly constitutes a contraindication to the use of this product.

WARNINGS
The benefits of transdermal nitroglycerin in patients with acute myocardial infarction or congestive heart failure have not been established. If one elects to use nitroglycerin in these conditions, careful clinical or hemodynamic monitoring must be used to avoid the hazards of hypotension and tachycardia.

A cardioverter/defibrillator should not be discharged through a paddle electrode that overlies a Transderm-Nitro patch. The arcing that may be seen in this situation is harmless in itself, but it may be associated with local current concentration that can cause damage to the paddles and burns to the patient.

PRECAUTIONS
General
Severe hypotension, particularly with upright posture, may occur with even small doses of nitroglycerin. This drug should therefore be used with caution in patients who may be volume depleted or who, for whatever reason, are already hypotensive. Hypotension induced by nitroglycerin may be accompanied by paradoxical bradycardia and increased angina pectoris.

Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

As tolerance to other forms of nitroglycerin develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted.

In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. Chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers, demonstrating the existence of true physical dependence.

Several clinical trials in patients with angina pectoris have evaluated nitroglycerin regimens which incorporated a 10-12 hour nitrate-free interval. In some of these trials, an increase in the frequency of anginal attacks during the nitrate-free interval was observed in a small number of patients. In one trial, patients demonstrated decreased exercise tolerance at the end of the nitrate-free interval. Hemodynamic rebound has been observed only rarely; on the other hand, few studies were so designed that rebound, if it had occurred, would have been detected. The importance of these observations to the routine, clinical use of transdermal nitroglycerin is unknown.

Information for Patients
Daily headaches sometimes accompany treatment with nitroglycerin. In patients who get these headaches, the headaches may be a marker of the activity of the drug. Patients should resist the temptation to avoid headaches by altering the schedule of their treatment with nitroglycerin, since loss of headache may be associated with simultaneous loss of antianginal efficacy.

Treatment with nitroglycerin may be associated with lightheadedness on standing, especially just after rising from a recumbent or seated position. This effect may be more frequent in patients who have also consumed alcohol.

After normal use, there is enough residual nitroglycerin in discarded patches that they are a potential hazard to children and pets.

A patient leaflet is supplied with the systems.

Drug Interactions
The vasodilating effects of nitroglycerin may be additive with those of other vasodilators. Alcohol, in particular, has been found to exhibit additive effects of this variety.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have examined the carcinogenic or mutagenic potential of nitroglycerin. Nitroglycerin's effect upon reproductive capacity is similarly unknown.

Pregnancy Category C
Animal reproduction studies have not been conducted with nitroglycerin. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitroglycerin is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Adverse reactions to nitroglycerin are generally dose-related, and almost all of these reactions are the result of nitroglycerin's activity as a vasodilator. Headache, which may be severe, is the most commonly reported side effect. Headache may be recurrent with each daily dose, especially at higher doses. Transient episodes of lightheadedness, occasionally related to blood pressure changes, may also occur. Hypotension occurs infrequently, but in some patients it may be severe enough to warrant discontinuation of therapy. Syncope, crescendo angina, and rebound hypertension have been reported but are uncommon.

Extremely rarely, ordinary doses of organic nitrates have caused methemoglobinemia in normal-seeming patients. Methemoglobinemia is so infrequent at these doses that further discussion of its diagnosis and treatment is deferred (see Overdosage).

Application-site irritation may occur but is rarely severe.

In two placebo-controlled trials of intermittent therapy with nitroglycerin patches at 0.2 to 0.8 mg/hr, the most frequent adverse reactions among 307 subjects were as follows:

	Placebo	Patch
Headache	18%	63%
Lightheadedness	4%	6%
Hypotension, and/or syncope	0%	4%
Increased angina	2%	2%

OVERDOSAGE
Hemodynamic Effects
The ill effects of nitroglycerin overdose are generally the result of nitroglycerin's capacity to induce vasodilatation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures; and death.

Laboratory determinations of serum levels of nitroglycerin and its metabolites are not widely available, and such determinations have, in any event, no established role in the management of nitroglycerin overdose.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of nitroglycerin and its active metabolites. Similarly, it is not known which, if any, of these substances can usefully be removed from the body by hemodialysis.

No specific antagonist to the vasodilator effects of nitroglycerin is known, and no intervention has been subject to controlled study as a therapy of nitroglycerin overdose. Because the hypotension associated with nitroglycerin overdose is the result of venodilatation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary.

The use of epinephrine or other arterial vasoconstrictors in this setting is likely to do more harm than good.

In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of nitroglycerin overdose in these patients may be subtle and difficult, and invasive monitoring may be required.

Methemoglobinemia
Nitrate ions liberated during metabolism of nitroglycerin can oxidize hemoglobin into methemoglobin. Even in patients totally without cytochrome b_5 reductase activity, however, and even assuming that the nitrate moieties of nitroglycerin are quantitatively applied to oxidation of hemoglobin, about 1 mg/kg of nitroglycerin should be required before any of these patients manifests clinically significant ($\geq$ 10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin should require even larger doses of nitroglycerin. In one study in which 36 patients received 2-4 weeks of continuous nitroglycerin therapy at 3.1 to 4.4 mg/hr, the average methemoglobin level measured was 0.2%; this was comparable to that observed in parallel patients who received placebo.

Notwithstanding these observations, there are case reports of significant methemoglobinemia in association with moderate overdoses of organic nitrates. None of the affected patients had been thought to be unusually susceptible.

Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adecuate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown, without color change on exposure to air.

When methemoglobinemia is diagnosed, the treatment of choice is methylene blue, 1-2 mg/kg intravenously.

DOSAGE AND ADMINISTRATION
The suggested starting dose is between 0.2 mg/hr*, and 0.4 mg/hr*. Doses between 0.4 mg/hr* and 0.8 mg/hr* have shown continued effectiveness for 10-12 hours daily for at least one month (the longest period studied) of intermittent administration. Although the minimum nitrate-free interval has not been defined, data show that a nitrate-free interval of 10-12 hours is sufficient (see INDICATIONS AND USAGE). Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily patch-on period of 12-14 hours and a daily patch-off period of 10-12 hours.

Although some well-controlled clinical trials using exercise tolerance testing have shown maintenance of effectiveness when patches are worn continuously, the large majority of such controlled trials have shown the development of tolerance (i.e., complete loss of effect) within the first 24 hours after therapy was initiated. Dose adjustment, even to levels much higher than generally used, did not restore efficacy.

PATIENT INSTRUCTIONS FOR APPLICATION OF SYSTEM
A patient leaflet is supplied with each carton.

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			**100 Systems	NDC 57267-902-30
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			**30 Systems	NDC 57267-905-42
			**100 Systems	NDC 57267-905-30
0.4 mg/hr	50 mg	20 cm²	30 Systems	NDC 57267-910-26
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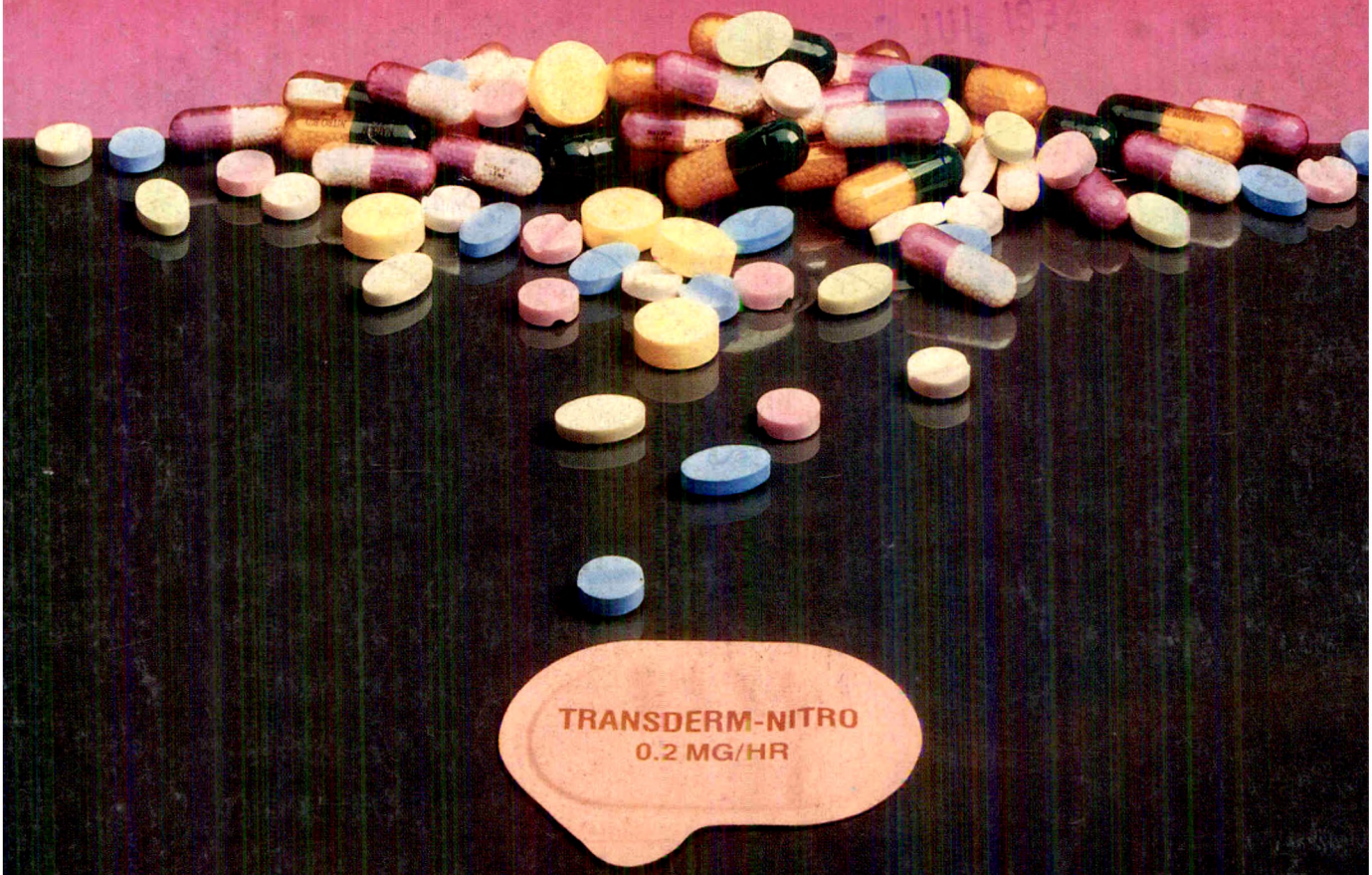
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1. Brady EM, Gold OG, Rosenbach HJ. Antianginal efficacy of transdermal nitroglycerin and oral nitrates: The ACTION Study. *Cardiovasc Rev Rep*. October 1988: 40-44.

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APRIL 2, 1992

A Symposium: Hypertension Management Strategies for the 1990s: Focus on Angiotensin-Converting Enzyme (ACE) Inhibition and Reduction of Cardiovascular Risk

GUEST EDITOR:

James A. Schoenberger, MD
Rush-Presbyterian St. Luke's Medical Center
Chicago, Illinois

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APRIL 2, 1992 VOL. 69 NO. 10

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GUEST EDITOR:
James A. Schoenberger, MD
Chairman, Department of Preventive Medicine
Rush-Presbyterian St. Luke's Medical Center
Chicago, Illinois

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A SYMPOSIUM: HYPERTENSION MANAGEMENT STRATEGIES FOR THE 1990s: FOCUS ON ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITION AND REDUCTION OF CARDIOVASCULAR RISK

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Introduction

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As we enter the last decade of the century, there no longer can be any doubt that treating hypertension and other cardiovascular risk factors lowers mortality and morbidity from cardiovascular disease and coronary artery disease. Since 1972, there has been more than a 50% decline in age-adjusted stroke mortality and a 35% decrease in coronary artery disease mortality. The major issue now is choosing the best treatment plan for reducing a particular patient's cardiovascular risk. In the past decade, we have learned that there is much more to reducing cardiovascular risk from high blood pressure than just lowering the pressure. The treatment strategy must also be designed to have minimal impact on the patient's lifestyle and quality of life, and we must take care not to decrease one risk factor at the expense of increasing another. Failure to take these considerations into account could result in lack of patient compliance and reduced benefit from the treatment program.

Today we have a veritable arsenal of drugs, including antihypertensive agents, antianginal agents, antiarrhythmic agents, and cholesterol-lowering agents, all of which are effective in some patients and not in others. Since the late 1970s, two new classes of drugs, the angiotensin-converting enzyme (ACE) inhibitors and the calcium channel blockers, have been added to this armamentarium. However, in the 1984 Report of the Joint Committee on the Detection, Evaluation, and Treatment of High Blood Pressure, only diuretics and beta blockade were recommended for first-line antihypertensive therapy. In the 1988 Report, the Joint Committee acknowledged that clinical experience obtained since the last report indicates that both ACE inhibition and calcium channel blockade are useful for initial therapy.

ACE inhibition, the focus of this symposium, has been shown to reduce cardiovascular risk without many of the adverse effects associated with diuretics, beta blockers, and alpha blockers. Of particular interest is evidence supporting the existence of local renin–angiotensin systems that appear to participate in cardiovascular homeostasis and in the pathogenesis of cardiovascular disorders. It has been shown that the blood pressure-lowering effects of ACE inhibition, particularly with the ACE inhibitor quinapril, could be correlated more closely with ACE inhibition in aortic tissue than with ACE inhibition in plasma. These and other aspects of reducing cardiovascular risk with ACE inhibition were presented at the 1990 Annual Session of the International College of Angiology and will be discussed and reviewed in this supplement.

We trust that the information provided by our distinguished faculty will provide valuable insights into these important issues.



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Angiotensin-Converting Enzyme in Cardiovascular and Adrenal Tissues and Implications for Successful Blood Pressure Management

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Components of the renin–angiotensin system, and the ability to synthesize these components locally, have been demonstrated in cardiovascular tissues. Locally generated angiotensin II may affect vascular tone, regional blood flow, cardiac contractility, and vascular and cardiac growth. Local renin–angiotensin systems may exert autocrine and paracrine functions, whereas the circulating system serves an endocrine function. Use of angiotensin-converting enzyme (ACE) inhibitors has provided further clarification of the activities of local renin–angiotensin systems. Tissue and systemic effects of these agents may prove equally important in determining their clinical efficacy. Experiments with quinapril demonstrated that inhibition of vascular ACE was a significant component of the antihypertensive effect of the drug. Differences at the tissue level may have implications for the efficacy and tolerability of a particular agent. Improved individualization of therapy may be accomplished by the use of newer ACE inhibitors with very favorable side effects profiles and tissue specificity. The newest agent, quinapril, appears to exert an important effect on vascular converting enzyme.

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Recent evidence strongly supports the existence of local renin–angiotensin systems that interact with the circulating renin–angiotensin system to regulate the function and growth of the vascular wall, the myocardium, and other tissues important in cardiovascular physiology. Such local renin–angiotensin systems are the focus of this review.

VASCULAR RENIN–ANGIOTENSIN SYSTEM

The existence of a local vascular renin–angiotensin system is suggested by the finding of the essential components of the renin–angiotensin system in the blood vessel wall.[1–4] Renin-like activity and angiotensins have been demonstrated in large and small arteries and in veins. Angiotensin receptors have been found in vascular smooth muscles and possibly in endothelial cells, whereas angiotensin-converting enzyme (ACE) is widespread on endothelial and possibly on smooth muscle cells. Moreover, renin-like activity persisted many hours after plasma renin activity could no longer be detected in animal studies.

Immunoreactive angiotensin may be found in the blood vessel wall due to local synthesis, uptake from plasma, or as a result of both processes. A substantial amount of the renin in the walls of large vessels appears to be taken up from the plasma. In contrast, the presence of renin and angiotensin messenger ribonucleic acid (mRNA) in vessel walls and the synthesis of renin mRNA and angiotensin by cultured vascular endothelial and smooth muscle cells indicate local production of renin–angiotensin components.[5]

Cardiac renin–angiotensin system: Components of the renin–angiotensin system, including renin activity, angiotensin and its binding site, and ACE, have also been detected in homogenates of the whole heart. Although biochemical detection of these components does not distinguish between uptake and local synthesis, molecular biological studies demonstrating the expression of the relevant genes suggest local synthesis. Renin and angiotensinogen mRNAs have been found in atrial and ventricular myocytes, providing convincing evidence of the existence of a local endogenous renin–angiotensin system.[6,7]

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TABLE I Autocrine and Paracrine Functions of the Vascular Renin-Angiotensin System

Cell Type	Autocrine Functions	Paracrine Functions
Smooth muscle	Vascular contraction	Norepinephrine release
Endothelial	Prostaglandin synthesis Possible EDRF release	Vascular contraction

EDRF = endothelial-derived relaxant factor.

TABLE II Effects of Angiotensin-Converting Enzyme Inhibitors on the Heart

- Secondary to effects on the vasculature
  - Coronary vasodilation
  - Systemic arterial and arteriolar dilation
  - Increased venous capacitance
- Primary to effects on the heart
  - Possible negative inotropism
  - Cardioprotective
    - Regression of ventricular hypertrophy and prevention of cardiac enlargement
    - Reduction of reperfusion-induced ventricular arrhythmias
- No adverse effects
  - Cardiac output
  - Heart rate

Function of the vascular renin–angiotensin system: An endogenous renin–angiotensin system may play a major role in the paracrine and autocrine functions of the vascular myocyte and endothelial cell, which influence vascular tone and therefore blood pressure. Vascular endothelial angiotensin may produce vasoconstriction by activating receptors on vascular smooth muscle cells and increasing sympathetic tone by facilitation of catecholamine release from noradrenergic nerve endings. The renin–angiotensin system also stimulates the synthesis and release of endothelial prostacyclin and endothelial-derived relaxing factor, both of which cause relaxation of vascular smooth muscle and vasodilation (Table I).[5]

The net effect (contraction or relaxation) may depend on the relative contributions of these mechanisms. Heterogenous vascular responses occur in different vascular beds and may be physiologically significant, as indicated by the observation that ACE inhibition produces different regional blood flow distribution patterns.[5]

Large arteries appear responsive to angiotensin II. Blockade of angiotensin II production with ACE inhibitors resulted in increased arterial compliance, further supporting the role of the local vascular renin–angiotensin system.[8]

The local vascular renin–angiotensin system may also contribute to cerebrovascular resistance and autoregulation of cerebral blood flow, the latter being the process by which cerebral blood flow is maintained relatively constant despite changes in arterial blood pressure. An abrupt increase in arterial pressure produces constriction of cerebral resistance vessels, whereas decreased pressure results in vasodilation. The ACE inhibitor captopril lowered the limits of autoregulation of cerebral blood flow in both normotensive and spontaneously hypertensive rats, which may explain the finding that cerebral blood flow is preserved despite significant reduction in blood pressure in patients which chronic heart failure.[9]

CARDIAC RENIN–ANGIOTENSIN SYSTEM

Although direct evidence is lacking, strong indirect support exists for the physiologic role of an endogenous cardiac renin–angiotensin system in regulating cardiac function. A variety of cardiac effects has been observed in response to administration of exogenous angiotensin. Perfusion of angiotensin I into isolated rat heart produced conversion to angiotensin II as measured in the coronary sinus. ACE inhibitors blocked this conversion.[6]

The regulation of the cardiac renin–angiotensin system itself seems to be tissue-specific, as indicated by the influence of sodium on tissues important in cardiovascular function and its lack of effect on non-cardiovascular systems. Sodium depletion resulted in increased renin and angiotensinogen mRNA in the heart, stimulation of renal and adrenal renin expression but not submandibular or testicular expression, and activation of cardiac and renal but not hepatic angiotensinogen mRNA.[6]

Possible physiologic roles of this local cardiac renin–angiotensin system include coronary vasoconstriction, increased cardiac contractility, production of myocardial hypertrophy and possibly hyperplasia, and adverse effects on myocardial metabolism and ventricular arrhythmias during ischemia and reperfusion injury. The use of ACE inhibitors, which produced a decreased incidence of arrhythmias in humans and cardioprotective effects in animals, further indicates the potential role for a cardiac renin–angiotensin system and has important clinical implications (Table II).[2,6]

The postulated autocrine and paracrine effects of local angiotensin II on cardiac contractility are similar to those related to vascular contractility. Use of ACE inhibitors in the isolated perfused rabbit heart with intact sympathetic nerves resulted in reduction of sympathetic effects, implying inhibition of locally generated angiotensin in the absence of exogenous angiotensins. However, it has not been clearly proven that cardiac angiotensin has a tonic effect on the myocardium in vivo.[4,10]

Local renin–angiotensin systems may also influence the development of cardiac hypertrophy. Evidence suggests that angiotensin can induce hypertrophy and possibly hyperplasia of vascular myocytes in hypertension, which can then contribute to the pathogenesis of cardiac hypertrophy. This evidence includes observations that angiotensin II produced mitogenic effects on fibroblast 3T3 cells in vitro and increased growth and proliferation of cultured vascular myocytes in serum. Angiotensin II also increased protein synthesis and cell mass in cultured

rat aorta smooth muscle in the quiescent, confluent phase. Additionally, the development of vascular hypertrophy in spontaneously hypertensive rats was prevented by treatment with the ACE inhibitor captopril.[4,6]

A prominent feature of hypertension is thickening of arteries and arterioles, predominantly related to increases in the total mass of smooth muscle cells. Hypertrophy and hyperplasia of the vascular myocyte produce an increased wall/lumen ratio, which can act as a positive feedback mechanism, perpetuating hypertension by fostering increased vascular tone. Additionally, an increase in the number of polyploid myocytes has been seen, which can produce increased cellular mass.[11,12]

The effects of vascular growth factors (shown to be produced by both smooth muscle and endothelial cells) may be responsible for some of the changes in the vasculature seen in hypertension. Morphologic and functional changes may occur in endothelial cells in the early phase of the development of hypertension. Growth factors from endothelial cells may then stimulate growth of vascular smooth muscles.[11]

ACE inhibition in patients with essential hypertension resulted in a significant increase in arterial diameters according to several reports. By contrast, in normal healthy volunteers, arterial diameter, blood flow, and indexes of arterial stiffness did not change. The contribution of vascular rather than circulating angiotensin in the mediation of arterial compliance was suggested by the observation that serum ACE activities were inhibited up to 95% in both experimental groups.[8]

ADRENAL RENIN–ANGIOTENSIN SYSTEM

The presence of angiotensinogen mRNA has been demonstrated in adrenal glands.[4] It is likely that adrenal angiotensin serves to regulate aldosterone biosynthesis. Support for the role of the adrenal renin–angiotensin system derives from observations that aldosterone secretion correlated closely with renin activity in rat adrenals, and adrenal renin levels were increased in spontaneously hypertensive rats. Furthermore, the angiotensin antagonist saralasin inhibited basal secretion of aldosterone in isolated adrenal glomerulosa cells.[4]

ACE inhibitors have been shown to have a direct effect on the local production of angiotensin II. In their study of the adrenal tissue effects of enalapril in rats placed on a low sodium diet, Braley et al[13] demonstrated a significant reduction of plasma aldosterone secreted by the isolated glomerulosa cells of 13 rats pretreated with the ACE inhibitor. These findings suggested a local effect on the production of angiotensin II.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE inhibitors are important therapeutic options for the treatment of patients with hypertension. ACE inhibition results in arteriolar dilation, which reduces total peripheral resistance and therefore decreases arterial blood pressure. Reflex expansion of intravascular volume and cardiac stimulation do not occur. Renal blood flow and glomerular filtration rate are preserved, while dilation of both efferent and afferent glomerular arterioles is produced with reduced glomerular hydrostatic pressure and renal filtration fraction. Cardiac mass and wall thickness are also reduced by ACE inhibitors, the actions of which appear to involve the autocrine/paracrine functions of local tissue renin–angiotensin systems.[3]

Mechanisms of action: The vascular and cardiac effects of ACE inhibitors may be the result of 1 of several mechanisms. They may inhibit the production of circulating or local converting enzyme, prevent bradykinin degradation, stimulate prostaglandin synthesis, or inhibit catecholamine release. Studies with a variety of agents suggest that the observed effects on coronary flow may be attributable to 2 mechanisms, 1 dependent on and the other independent of ACE activity.[6]

Vascular effects: Among the vascular effects of ACE inhibition is the increase in arterial compliance seen with both short- and long-term administration of these agents, whereas therapy with captopril and enalapril produced increased compliance in the systemic and brachial circulations. This augmentation by ACE inhibitors of the buffering effect of large arteries may reduce vascular injury from the shear force of hypertension (which may initiate the atherosclerotic process in these vessels).[8]

ACE inhibitors can also reduce vascular and cardiac hypertrophy in hypertension. Captopril (but not propranolol or hydralazine) prevented the development of vascular hypertrophy in spontaneously hypertensive rats in vivo. ACE inhibitors reduced both cardiac hypertrophy and blood pressure, whereas hydralazine reduced blood pressure but did not affect ventricular hypertrophy.[4]

Heart effects: ACE inhibitors have also been shown to produce vasodilatory effects in isolated perfused rat hearts independent of circulating angiotensin II (which causes coronary vasoconstriction). This vasodilation may have resulted from blockade of production of coronary vascular tissue angiotensin II, or activation of other mechanisms, such as biosynthesis of vasodilatory prostaglandin.[6]

In addition to their vascular effects, ACE inhibitors can induce regression of ventricular hypertrophy, prevent ventricular enlargement, and reduce reperfusion injury-induced ventricular arrhythmias, among other cardioprotective effects. The effects of the ACE inhibitor were presumably on local tissue systems, as implied by the use of the isolated rather than in situ preparation.[4,6,10]

Tissue effects and efficacy: Experiments with the ACE inhibitor quinapril suggest that inhibition of vascular ACE was more important than plasma inhibition in

the antihypertensive effect of the drug. Plasma and tissue ACE activity were inhibited in a dose-dependent manner but whole brain ACE activity was not altered. Inhibition of plasma activity did not correlate well with the antihypertensive effect of quinapril, whereas aortic ACE inhibition was better correlated[14] (Figure 1). These results are consistent with the hypothesis that tissue ACE inhibition is the major site of action for quinapril.

Adverse effects: ACE inhibitors as a class seem to be generally free of serious side effects. Cough, an annoying side effect, disappears with discontinuation of the drug. A possible mechanism is the increased level of circulating kinins from ACE inhibitor activity. There appear to be no adverse effects on serum lipid levels, carbohydrate metabolism, or potassium and uric acid levels. However, there is a risk of renal failure in some patients with bilateral renal arterial disease or unilateral disease with 1 kidney, as the autocrine/paracrine autoregulatory adaptive mechanisms of the opposite kidney are lacking.[3]

It has also been shown in patients with severe chronic heart failure[15] and in others with hypertension[16] that enalapril may have more adverse effects on renal function than captopril or quinapril. In 16 patients treated with captopril the mean creatinine clearance was 55.2 ± 6.8 mL/min, whereas in 18 patients treated with enalapril the mean creatinine clearance was 44.2 ± 5.3 mL/min.[15] In hypertensive patients (586 in all), the investigators found that twice-daily dosing with quinapril or enalapril resulted in elevated serum creatinine levels in 6 and 8% of patients, respectively. On the other hand, with once-daily dosing elevated serum creatinine was found in 1% of quinapril patients but in 5% of enalapril patients. These data were taken to suggest that once-daily dosing with quinapril permitted restoration of glomerular filtration pressure before the next scheduled dosing.[16]

TABLE III The "Ideal" Antihypertensive Agent

Efficacy in suitable clinically identifiable patient groups
Efficacy as monotherapy
Well tolerated
Low incidence of side effects, especially on lipid levels and quality of life
Convenient adminstration
Action compatible with other antihypertensive agents
Cost-effective and low total cost

MANAGEMENT OF HYPERTENSION

The mechanisms of action of currently available antihypertensive agents vary, as do the pathophysiologic processes responsible for hypertension. Five classes of agents—ACE inhibitors, β blockers, calcium antagonists, peripheral α-adrenergic receptor blockers, and thiazide diuretics—may be appropriate monotherapy in selected patients. Because of the differences among these agents, therapy can be individualized on the basis of such factors as patient age, sex, and race; existence of concomitant disease; prior antihypertensive treatment (effectiveness and presence of side effects); and type of hypertension.

Individualization of therapy: The "ideal" antihypertensive agent should be characterized by proven efficacy (alone or in combination with other agents) in a suitable clinically identifiable group of patients. Blood pressure-lowering effects should not be accompanied by significant metabolic side effects (particularly on blood lipid levels). Administration of this agent should not impair other organ systems or the patient's quality of life. Convenience of administration and titration (with a dose–response profile that allows ease of titration without additional side effects), action compatible with that of other antihypertensive drugs, cost-effectiveness, and ready availability at low total cost are other important characteristics of the ideal agent (Table III).[17,18]

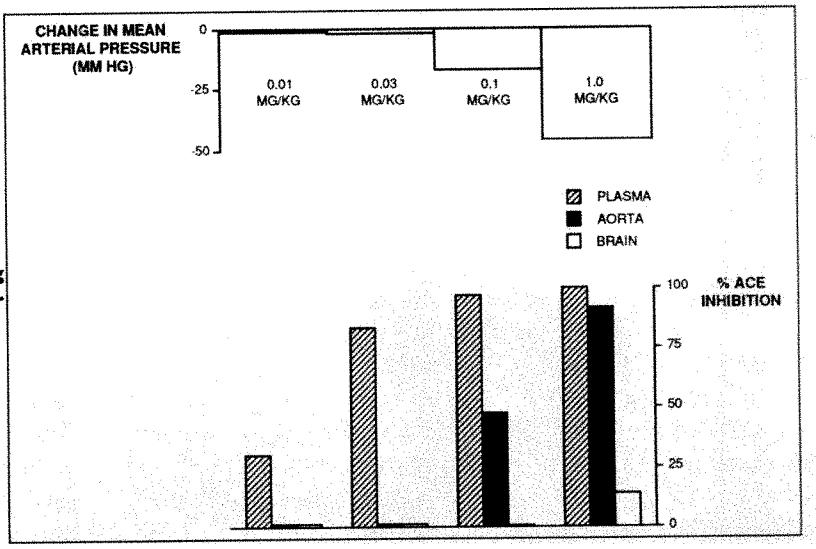


FIGURE 1. Relation between blood pressure reduction and angiotensin–converting enzyme (ACE) inhibition in plasma and tissues with increasing doses of quinapril in rats. (From Kaplan et al.[14])

TABLE IV Serum Lipids and Lipoproteins in Hypertensive Patients (n = 16) Treated with Quinapril for One Year

	Baseline (mmol/liter)	One Year* (mmol/liter)
Cholesterol	6.1	6.3
Triglycerides	2.3	2.2
HDL	1.28	1.26
LDL	4.1	4.2
HDL/LDL	0.34	0.34

Reproduced by permission from Koskinen et al.[19]
* Differences between baseline and 1-year values were not statistically significant.
HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol.

Vasodilators and angiotensin-converting enzyme inhibitors: Among the available antihypertensive agents, vasodilators (ACE inhibitors, α-adrenergic receptor antagonists, and calcium antagonists) possess desirable characteristics that make them particularly suitable for initial therapy in many patients with hypertension. They specifically correct a basic pathophysiologic abnormality of hypertension by decreasing systemic vascular resistance.

Vasodilators do not adversely affect cardiac performance during physical activity, an important trait in view of the utility of the nonpharmacologic therapy of regular exercise. They may favorably influence the development of left ventricular hypertrophy, considered to be an independent and significant risk factor for subsequent cardiovascular mortality and morbidity.[17]

Moreover, the potential cardioprotective effect of ACE inhibitors, the hypocholesterolemic effect of α-adrenergic receptor antagonists, and the beneficial effect of calcium antagonists on left ventricular function add further support to the use of these agents. An additional major benefit of ACE inhibitors is that they affect a specific mechanism regarded as important in the pathogenesis of hypertension. Blockade of tissue as well as circulating ACE may contribute to their efficacy and specificity.[3,17]

Adverse effects: A substantial portion of the hypertensive population has elevated plasma total cholesterol levels and may therefore require pharmacologic therapy for hypercholesterolemia. However, drug-induced increases in blood lipid levels may carry the same risk as dietary increases. It is important, therefore, that the ACE inhibitors captopril, enalapril, and quinapril do not appear to affect atherogenic blood lipoprotein levels adversely (Table IV).[19]

The side effects profiles of ACE inhibitors (e.g., captopril, enalapril, and quinapril) are generally favorable. In addition to cough, common side effects are headache, dizziness, fatigue, and nausea and vomiting. Angioedema is a rare but potentially serious side effect also.[20,21]

Although quinapril had the lowest incidence of side effects compared to captopril and enalapril in double-blind studies, all of these agents were well tolerated.[20] Analysis of quinapril in 2,010 patients showed the drug to be equally well tolerated in young and elderly hypertensive patients, with a low incidence of rash and no neutropenia or agranulocytosis. The incidence and magnitude of hypotension and proportion of patients with "first-dose" hypotension or symptomatic hypotension was similar to that reported for captopril and enalapril.[22] In another comparative study of enalapril and quinapril in mild-to-moderate hypertension, more patients withdrew because of adverse effects with enalapril, suggesting that quinapril may have a somewhat better side effects profile.[23]

Cost of treatment: The total cost of therapy involves more than initial drug costs. It includes costs of laboratory monitoring and additional treatment of complications of therapy. Against these costs must be balanced the "savings" in terms of prevention of sequelae of hypertension, improvement in quality of life, and possible extension of life.[17]

Although ACE inhibitors may be more costly in terms of initial drug cost, they probably prove less costly for many patients in the long term compared to other antihypertensive agents, because they attack a basic cause of hypertension, and have a very favorable side effects profile.

Differences among angiotensin–converting enzyme inhibitors: Individual ACE inhibitors may differ in their effects on specific local renin–angiotensin systems and in their side effects profile. The advent of newer agents, particularly those with improved side effects profiles, e.g., quinapril, will allow for further individualization of therapy. Future knowledge about the circulating and local renin–angiotensin systems should assist in designing treatment tailored to the needs of the individual patient.[24]

CONCLUSION

ACE inhibitors appear to exert their principal action at local tissue sites. Differences among these agents may be related to differences in inhibition of converting enzyme produced at the tissue level: this may have important implications for the efficacy and tolerability of a drug. Management of hypertension and design of new drugs will probably need to be based on considerations of the activity of potential therapeutic agents at both the circulating and local levels of the renin–angiotensin systems.

In the heart, it has been shown that local angiotensin may influence both myocardial function and growth. The development of cardiac hypertrophy in patients with hypertension may be related to the activities of both

cardiac and vascular renin–angiotensin systems. Use of ACE inhibitors has added further evidence for the role of local renin–angiotensin systems in cardiovascular physiology and pathophysiology.

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Comparative Pharmacokinetics of Captopril, Enalapril, and Quinapril

Victor Vertes, MD, and Robert Haynie, MD, PhD

This review compares the metabolism and pharmacokinetic profiles of captopril, the first orally active angiotensin-converting enzyme (ACE) inhibitor, and 2 newer ACE inhibitors, enalapril and quinapril. Captopril differs from both enalapril and quinapril in that its chemical structure contains a sulfhydryl group, the presence of which may be important in the development of adverse reactions. Captopril also differs from enalapril and quinapril in its ability to be metabolized in plasma. Enalapril and quinapril are both de-esterified, most likely in the liver, to their active metabolites, enalaprilat and quinaprilat. All 3 ACE inhibitors are eliminated primarily via renal excretion, and renal dysfunction markedly increases the area under the time versus plasma concentration curves. Hepatic dysfunction also slows the conversion of enalapril and quinapril to their active metabolites. There is evidence that both captopril and enalapril, but not quinapril, may accumulate with repeated dosing. The pharmacokinetics of these agents are not significantly modified by co-administration of other drugs. However, captopril does cause marked increases in trough plasma levels of digoxin. Overall, the pharmacokinetic profiles of captopril, enalapril, and quinapril make them suitable for a wide range of patients with hypertension or congestive heart failure.

(Am J Cardiol 1992;69:8C–16C)

Control of hypertension is a key factor in reducing the risk of cardiovascular morbidity, disability, and premature death.[1] Administration of angiotensin-converting enzyme (ACE) inhibitors is 1 of the newest medical approaches to the treatment of hypertension, and this class of drugs is becoming an increasingly popular first choice in pharmacologic management.[2,3] ACE inhibitors are prescribed to greater numbers of a wider variety of patients with hypertension.

Informed decisions as to which of the agents in this class is most appropriate for a particular patient should take into account the metabolism, pharmacokinetics, and potential drug–drug interactions of the agents under consideration. Whereas the metabolism and pharmacokinetic properties of captopril, enalapril, and quinapril have all been described singly,[4–7] they have never been summarized and compared in a single report. This review provides such a comparison.

THE PHYSICAL CHEMISTRY OF CAPTOPRIL, ENALAPRIL, AND QUINAPRIL

The structural formulas of captopril, enalapril, and quinapril are shown in Figure 1. Captopril (1-[(2*S*)-3-mercapto-2-methylpropional]-L-proline), the first orally active ACE inhibitor, contains a sulfhydryl group that distinguishes it from both enalapril and quinapril. This difference may be important with respect to potentially adverse reactions since sulfhydryl compounds have been associated with a high incidence of undesirable side effects such as taste disturbances, rash, nephropathy, and neutropenia.[3] Rash has been observed in about 5% of all patients treated with captopril.[8] In contrast, a recent review[9] reported that only 2% of a sample of over 2,000 patients treated with quinapril experienced dermatologic reactions.

Enalapril maleate (1-[N-[1-(*S*)-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline, (*Z*)-2-butenedioate (1:1) salt) is a relatively weak nonsulfhydryl ACE inhibitor. It is readily hydrolyzed to its more potent metabolite, enalaprilat, thereby achieving significant inhibition of ACE activity.[10]

Quinapril hydrochloride ([3*S*-[2(*R**)-(*R**)]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid monohydrochloride) is an orally active nonpeptide, nonsulfhydryl ACE inhibitor. It contains a tetrahydroquino-

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lone moiety and is an isomer with the *S* configuration at all 3 asymmetric carbons. Like enalapril, quinapril must be de-esterified to its major metabolite, quinaprilat, to develop a high degree of ACE inhibitory activity.[7] However, quinapril has nearly 400 times more ACE inhibitory activity than enalapril (Table I).

TABLE I In Vitro Inhibition of Unpurified Angiotensin-Converting Enzyme from Guinea Pig Serum and Human Placenta

Compound	Guinea Pig	IC_{50} (M) Normotensive Human	Hypertensive Human
Quinapril	8.3×10^{-9} (4)	8.4×10^{-8} (3)	8.2×10^{-8} (3)
Quinaprilat	2.8×10^{-9} (4)	6.4×10^{-10} (3)	5.9×10^{-10} (3)
Enalapril	1.4×10^{-7} (4)	4.0×10^{-7} (3)	3.2×10^{-7} (3)
Enalaprilat	3.1×10^{-9} (4)	4.3×10^{-10} (3)	3.8×10^{-10} (2)
Captopril	1.3×10^{-8} (4)	1.2×10^{-9} (3)	Not tested

Reproduced by permission from Kaplan et al.[7]
The number of concentration-response curves for each compound is shown in parentheses.
IC_{50} (M) = concentration of compound to produce 50% inhibition of converting enzyme activity.

THE METABOLISM OF CAPTOPRIL, ENALAPRIL, AND QUINAPRIL

The metabolism of captopril is relatively complex. After absorption, it is oxidized in plasma to several forms, including a disulfide dimer and mixed disulfides with endogenous thiol compounds. It is also likely that captopril and its pool of metabolites undergo reversible interconversions.[11,12] Captopril and its metabolites are excreted primarily by the kidneys, with lesser elimination in feces. Kripalani et al[13] reported that 86% of the total radioactivity administered in the form of labeled captopril was recovered in the urine (68%) and feces (18%). The 24-hour urinary samples consisted of 58% unchanged drug, 2% captopril disulfide, and 40% unidentified polar metabolites. Studies in rats administered radiolabeled captopril[11] have demonstrated that the drug is distributed throughout the entire body with the exception of the central nervous system.

The metabolism and excretion of enalapril and quinapril are quite similar and somewhat simpler than those of captopril. Enalapril is absorbed by the gastrointestinal tract and is de-esterified in the liver to its active form, enalaprilat. Postabsorptive hydrolysis may also occur in the mucosal lining of the gastrointestinal tract, but this has not as yet been confirmed.[11] Ulm et al[10] reported that 94% of the administered dose of radiolabeled enalapril is recovered as either enalapril or enalaprilat. Thus, in contrast to the multiple metabolites of captopril, enalapril appears to have only 1 major metabolite. As in the case of captopril, excretion of enalapril and enalaprilat is primarily renal, with recovery of 61% of the administered dose of enalapril in urine—18% in the form of enalapril and 43% as enalaprilat. In addition, 33% of the administered dose is recovered in feces (enalapril = 6% and enalaprilat = 27%).

After either oral or intravenous administration in the rat and guinea pig, quinapril is metabolized to quinaprilat by nonspecific esterases that are not present in human plasma, suggesting that conversion of the parent compound to quinaprilat probably occurs in the liver or gastrointestinal tract in humans.[7] The fact that hepatic insufficiency associated with cirrhosis slows conversion of quinapril to quinaprilat[14] is consistent with the conclusion that the primary step in human quinapril metabolism occurs in the liver. In addition to quinaprilat, there are 2 minor and inactive diketopiperazine metabolites of quinapril, PD 109488 and PD 113413.[7]

After [^{14}C]quinapril is administered either orally or intraperitoneally, radiolabel distributes rapidly and extensively to all tissues except brain.[14] Radiolabel is also rapidly lost from all tissues except those rich in ACE (e.g., lung and kidney). The primary route for quinapril and quinaprilat elimination is renal. An important proportion of the drug is eliminated in the feces, however, as demonstrated by the recovery of radiolabel after administration of [^{14}C]quinapril in healthy human volunteers: 61% of radiolabel was recovered in the urine and 37% in the feces.[14] This observation may have some significance for the treatment of hypertensive patients with mild to moderate renal failure, because the biliary route of elimi-

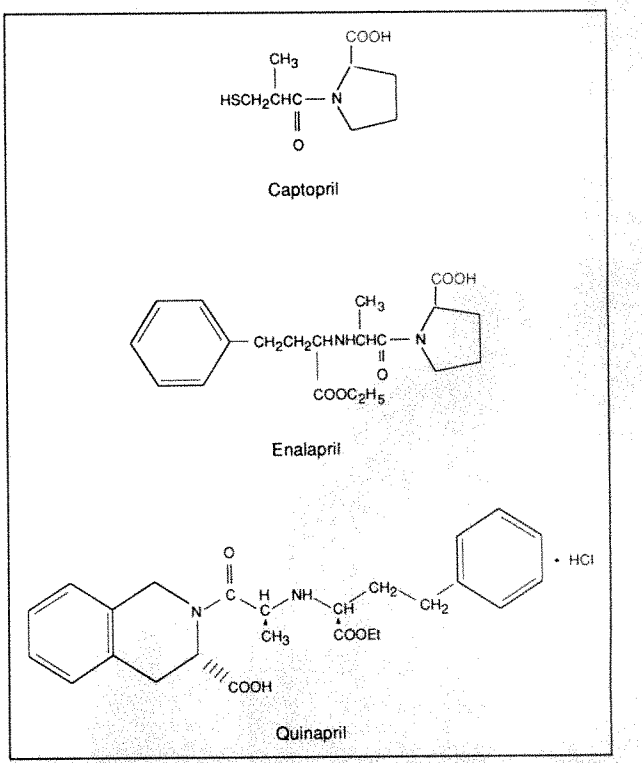


FIGURE 1. Structural formulas of captopril, enalapril, and quinapril.

nation may counteract any tendency for a build-up of the drug due to renal insufficiency.

PHARMACOKINETICS OF CAPTOPRIL, ENALAPRIL, AND QUINAPRIL IN NORMAL SUBJECTS

The pharmacokinetic properties of enalapril and quinapril are straightforward and compatible with single-compartment models. Maximum plasma concentration (C_{max}) and area under the curve from zero to infinity ($AUC_{0-\infty}$) are linearly related to dose whereas elimination half-life ($t_{1/2}$) is independent of dose.

The pharmacokinetics of orally administered captopril have been evaluated by several investigators.[13,15,16] Its pharmacokinetic profile, including both its C_{max} and $AUC_{0-\infty}$, is linear for doses ranging between 10 and 150 mg. Kripalani et al[13] reported that, after oral administration of 100 mg of [^{35}S]captopril, the C_{max} for unchanged drug in the blood was 800 ng/mL and the $AUC_{0-\infty}$ was 1,150 ng × hour/mL. The values for total radioactivity (captopril and all of its metabolites) were 1,580 ng/mL and 7,160 ng × hour/mL, respectively. Time to maximum concentration (T_{max}) for captopril and for total radioactivity was 1 hour. The time versus plasma concentration curves from this study are shown in Figure 2. Because captopril has an extensive metabolism, analysis of the elimination of this drug requires a triexponential model. The half-life for the β phase of elimination is reported to be 1.93 hours.[15]

The pharmacokinetic properties of enalapril in healthy subjects have also been described by a number of investigators.[17–20] The observations of Swanson et al[17] are typical. These investigators administered 40 mg enalapril to 12 healthy individuals, 23–37 years of age, and measured enalaprilat concentrations in serum (Figure 3). Values for C_{max}, T_{max} and AUC from 0–24 hours (AUC_{0-24}) were 154 ng/mL, 3.3 hours, and 1,209 ng × hour/mL, respectively. More recently, Ishizaki et al[19] administered 10 mg enalapril orally to 7 healthy subjects, aged 27–39 years, and used radioimmunoassay to determine serum levels of enalapril and enalaprilat. In this study, C_{max} values for enalapril and enalaprilat were 66.9 and 46.1 ng/mL, respectively. The T_{max} for enalapril was 1.0 hour and for enalaprilat it was 3.7 hours. $AUC_{0-\infty}$ also differed for enalapril (122.9 ng × hour/mL) and enalaprilat (375.4 ng × hour/mL). The elimination half-lives of enalapril and its primary metabolite were 0.63 and 3.88 hours, respectively.

Olson et al[6] have carried out the most extensive pharmacokinetic study of quinapril to date. They administered single oral doses ranging from 2.5 to 80 mg in healthy volunteers, aged 21–72 years, and evaluated plasma concentrations of both quinapril and quinaprilat. Mean plasma concentration versus time profiles for quinaprilat at each dose of the parent drug are shown in Figure 4. Both C_{max} and $AUC_{0-\infty}$ were directly proportional to amount of drug administered (Table II). There was no detectable concentration of quinapril after the 2.5 mg dose because of its rapid conversion to quinaprilat. After the 80-mg dose, C_{max} for quinapril was 536 ng/

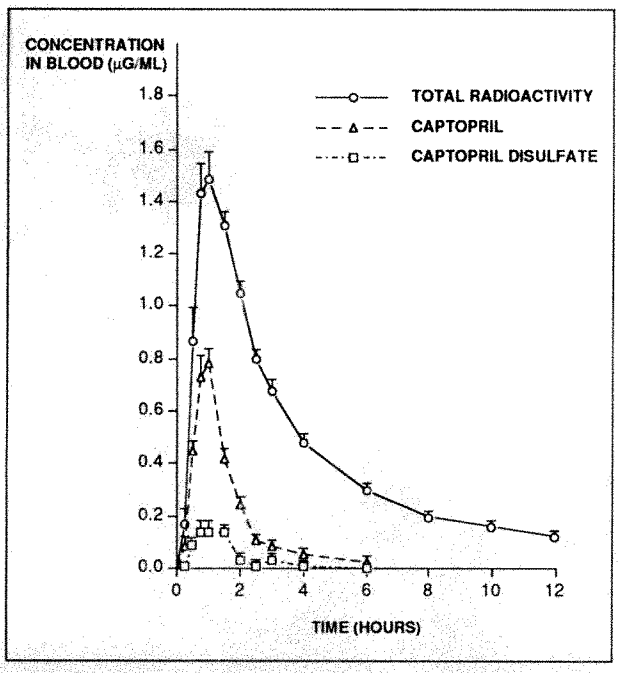


FIGURE 2. Mean ± standard error of the mean of concentrations of total radioactivity, captopril, and captopril disulfide in blood (n = 10). (From Kripalani et al.[13])

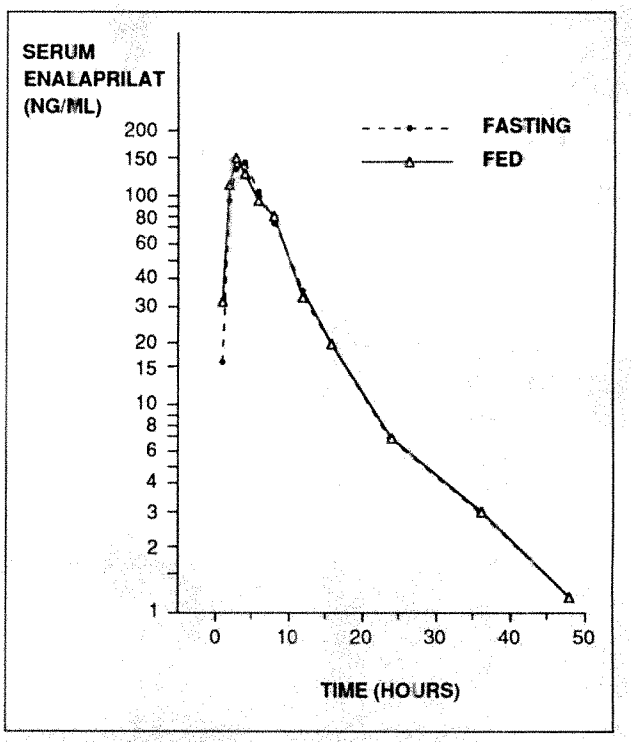


FIGURE 3. Mean enalaprilat serum concentrations after administration of 40 mg enalapril maleate to fasting and fed healthy subjects (n = 12). (From Swanson et al.[17])

TABLE II Mean (RSD%) Quinapril and Quinaprilat Pharmacokinetic Parameter Values Obtained for 2.5, 10, 40, and 80 mg Quinapril Administered as Single Daily Doses

Parameter	Quinapril Dose (mg)			
	2.5	10	40	80
C_{max} (ng/mL)				
Quinapril	ND	65 (46)	207 (43)	536 (73)
Quinaprilat	41 (31)	223 (27)	923 (30)	1,760 (45)
T_{max} (hours)				
Quinapril	ND	0.7 (36)	1.4 (56)	0.9 (60)
Quinaprilat	2.1 (35)	1.6 (23)	2.3 (39)	1.5 (22)
$AUC_{0-\infty}$ (ng × hour/mL)				
Quinapril	ND	93 (42)	363(41)	677(53)
Quinaprilat	167 (35)	803 (29)	3,386(29)	6,212(43)
λz (hours^{-1})				
Quinapril	ND	0.894 (32)	0.753 (31)	0.835 (29)
Quinaprilat	0.334 (21)	0.376 (19)	0.365 (16)	0.368 (20)
$t_{1/2}$ (hours)				
Quinapril	ND	0.78	0.92	0.83
Quinaprilat	2.1	1.8	1.9	1.9
Ae_{0-72} (%)				
Quinapril	ND	3.7 (40)	3.1 (38)	3.4 (54)
Quinaprilat	25 (26)	29 (33)	27 (42)	29 (35)

Reproduced by permission from Olson et al.[6]
Ae_{0-72} = urinary excretion from time 0 to 72 hours after dose expressed as a percent of dose; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma concentration; ND = not determined because of low concentrations; RSD% = percent relative standard deviation; T_{max} = time of C_{max}; $t_{1/2}$ = apparent elimination half-life; z = apparent elimination rate constant.

mL. The C_{max} values for quinaprilat at these 2 doses of the parent drug were 41 and 1,760 ng/mL, respectively. There was no AUC for quinapril at the 2.5 mg dose compared with an $AUC_{0-\infty}$ of 677 ng × hour/mL for the 80 mg dose. The values for quinaprilat at these 2 doses were 167 and 6,212 ng × hour/mL, respectively. Both T_{max} and $t_{1/2}$ were independent of drug dose. Times to maximum concentration ranged between 0.7 and 1.4 hours for quinapril and 1.5 and 2.3 hours for quinaprilat. The elimination half-lives for quinapril varied between 0.78 and 0.92 hour and those for quinaprilat ranged between 1.8 and 2.1 hours. Ferry et al[21] evaluated the pharmacokinetics of a 40-mg oral dose of quinapril in healthy males, aged 22–49 years, and reported results quite similar to those of Olson et al.[6]

While the single-dose pharmacokinetics of enalapril and quinapril appear to be very similar, some differences are apparent with repeated dosing. Olson et al[6] have demonstrated that there is no accumulation of quinapril or quinaprilat when 20 mg of the parent drug is administered daily for 4 days. Lees and Reid[18] observed a >50% increase in C_{max} for plasma enalaprilat after administration of 10 mg of the parent drug to healthy volunteers for a period of 8 days. There was also a significant reduction in T_{max} after repeated administrations of enalapril. Currently, it is unclear whether captopril accumulates with repeated dosing. McKinstry et al[22] observed no accumulation during 10 days of administration of captopril (300 mg/day) to hypertensive patients with normal renal function. On the other hand, Jarrot et al[23] reported a significant increase in the AUC for unchanged captopril after 6 months of treatment in hypertensive patients.

PHARMACOKINETICS OF CAPTOPRIL, ENALAPRIL, AND QUINAPRIL IN SPECIAL PATIENT POPULATIONS

Special care must be taken to ensure that dosing of any drug, especially those that influence cardiovascular function, is commensurate with any changes in pharmacokinetic profiles that might occur with age or any other conditions that might be expected to impair metabolic function.

The pharmacokinetic profile of captopril is apparently unaffected by age. Creasey et al[24] reported that values

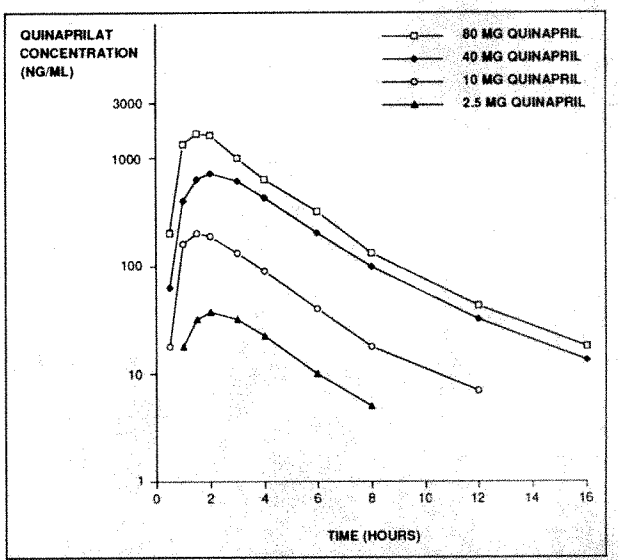


FIGURE 4. Mean plasma quinaprilat concentration-time profiles obtained after single 2.5, 10, 40, and 80 mg doses of quinapril. (From Olson et al.[6])

TABLE III Individual Oral Enalapril Kinetic Parameters in Young and Elderly Subjects

	AUC ng × hour/mL	T_{max} (hrs)	C_{max} (ng/mL)	CL/F*	F
Young subjects					
Y1	1,097	2	129	9.12	0.81
Y2	591	4	48	16.92	—
Y3	554	2	40	18.05	0.36
Y4	768	8	64	13.02	0.55
Y5	707	4	64	14.14	0.59
Y6	763	4	105	13.11	0.77
Y7	476	6	50	21.01	0.55
Y8	657	4	54	15.22	0.48
Y9	889	4	60	11.25	0.82
Mean ± SD	772 ± 188	3 ± 1	68 ± 29	14.65 ± 3.62	0.62 ± 0.16
Elderly subjects					
E1	820	2	197	12.20	0.82
E2	1,253	4	83	7.98	0.65
E3	1,046	2	120	9.56	0.65
E4	710	8	142	14.08	0.39
E5	1,746	4	36	5.73	0.84
E6	714	4	149	14.01	0.53
E7	867	6	59	11.53	0.44
E8	938	4	47	10.66	0.61
E9	877	4	77	11.40	0.60
Mean ± SD	997 ± 332	4 ± 2	101 ± 54	10.79 ± 2.72	0.61 ± 0.15
p value	<0.05	NS	NS	<0.05	NS

Reproduced by permission from Hockings et al.[25]
CL = clearance; F = absolute bioavailability; NS = not significant; SD = standard deviation; other abbreviations as in Table II.

for C_{max}, T_{max}, AUC and $t_{1/2\beta}$ in healthy subjects between 65 and 76 years of age given 100 mg of captopril in a single oral dose were not significantly different from those observed for an historical control group of healthy subjects between 18 and 35 years of age. This was true although there was a 36% reduction in renal clearance in the elderly volunteers.

Hockings et al[25] compared the pharmacokinetics of enalapril and enalaprilat in 9 healthy volunteers aged 22–30 with those in elderly subjects between 65 and 73 years of age. The AUCs for both enalapril and enalaprilat were significantly increased in the elderly subjects (Table III). These changes were associated with significant reductions in the clearance of both the parent drug and its major metabolite in the elderly subjects. Hockings et al[25] concluded that these pharmacokinetic changes were most likely the result of an age-related decline in renal function. The findings of Hockings et al[25] have been confirmed recently by Lees and Reid.[18]

The pharmacokinetic profile of quinapril changes slightly in elderly patients, but the alterations that have been observed are all predictable based on the reductions in renal function observed in these individuals. Two studies[14] have compared the pharmacokinetic profiles of quinapril in 29 elderly individuals (average age = 73 years) with moderate hypertension and in 30 young subjects (average age = 25 years). Creatinine clearance, used to assess renal function in both groups, averaged 99 and 62 mL/min in the younger and older subjects, respectively. In the elderly patients, there was a decrease in both the hydrolysis of quinapril to quinaprilat and in the elimination of quinaprilat. The net result of these 2 changes was a 27% increase in the C_{max} and a 50% increase in the $AUC_{0-\infty}$ in the older patients. The decreased rate of quinapril elimination in the older patients was well predicted on the basis of changes in renal function. Thus, as in the case of enalapril, declining renal function associated with advancing age rather than age itself is the primary cause of the change in the pharmacokinetic profile of quinapril in elderly patients. Clinically, quinapril has been shown to be equally effective in elderly and younger hypertensive patients.

Since renal excretion is the primary means of elimination of captopril, enalapril, and quinapril, it is not surprising that renal insufficiency has been shown to alter the pharmacokinetic profiles of these agents.

Studies involving captopril[26] have shown that absorption of the drug is generally not altered in patients with renal impairment but that clearance of the drug is significantly reduced and closely correlates with the degree of renal impairment determined by measurements of creatinine clearance.[26,27] Reduced captopril clearance results in significant increases in AUC for patients with renal insufficiency; captopril doses for such individuals should be reduced.

Renal insufficiency also alters the pharmacokinetic profiles of enalapril and enalaprilat.[28–30] Reduced clearance of both the parent drug and its metabolite and large increases in the AUC have been observed in patients with renal insufficiency who have been treated with enalapril. For example, Lowenthal et al[28] reported that AUC from 0 to 48 hours (AUC_{0-48}) for enalaprilat was 409 ng ×

hour/mL in healthy subjects receiving a 10-mg dose of enalapril, compared with 1,986 ng × hour/mL in patients with mild to moderate renal insufficiency (Figure 5). Thus, as for captopril, the dosing regimen of enalapril in patients with renal impairment should be adjusted to reflect the reduced clearance of both the parent drug and its metabolite. In a related study, Baba et al[31] demonstrated that the renal clearance of enalaprilat was reduced and AUC_{0-24} increased in diabetic patients with persistent proteinuria and reduced glomerular filtration rates.

Because of the similarities in the metabolism of enalapril and quinapril, it is not surprising that clearance of quinapril is also somewhat reduced in patients with renal insufficiency. Horvath et al[32] administered 20-mg oral doses of quinapril for 7 days to patients with normal renal function or mild, moderate, or severe renal impairment. These investigators observed that impaired renal function was associated with small decreases in quinapril clearance, which ranged between 2,095 mL/min in subjects with normal renal function and 1,255 mL/min in patients with severe renal dysfunction. As might be expected, this change was associated with a significant increase in quinapril $AUC_{0-\infty}$ to 166 ng × hour/mL in normal subjects and 296 ng × hour/mL for the patients with severe renal insufficiency. Similar changes were observed for quinaprilat. Clearance of this metabolite was 191 mL/min in normal subjects and 21 mL/min in patients with severe renal dysfunction. The $AUC_{0-\infty}$ for quinaprilat in these 2 groups was 1,856 and 18,700 ng × hour/mL, respectively. The elimination half-life of quinaprilat in normal patients was 2.3 hours compared to 11.6 hours in patients with severe renal impairment.

In summary, patients with renal insufficiency exhibit decreases in the elimination of captopril, enalapril, and quinapril. These data indicate that doses of all 3 drugs should be reduced in patients with renal impairment.

Hepatic insufficiency markedly alters the metabolism and thus the pharmacokinetics of numerous drugs. Therefore, it might be expected that hepatic dysfunction would change the pharmacokinetic profiles of both enalapril and quinapril since they are hydrolyzed to their active metabolites in the liver. Captopril, on the other hand, is metabolized in plasma, and hepatic dysfunction might be less likely to alter its pharmacokinetic profile. Larmour et al[33] have shown that the de-esterification of enalapril in vitro is slowed in patients with a history of hepatic dysfunction. Ohnishi et al[20] demonstrated the same effect on the metabolism of enalapril in patients with cirrhosis. In these patients, C_{max} and AUC were significantly increased for enalapril and were significantly decreased for enalaprilat. The pharmacokinetics of quinapril and quinaprilat have been examined in a small number of patients with hepatic insufficiency resulting from cirrhosis.[14] In these patients, a reduced rate and extent of quinapril hydrolysis to quinaprilat were associated with higher plasma concentrations of quinapril and lower plasma concentrations of quinaprilat. The subsequent elimination of quinaprilat was unaffected in these patients. To our knowledge, the effects of hepatic insufficiency on the pharmacokinetics of captopril have not been examined.

The pharmacokinetic profiles of captopril, enalapril, and quinapril have been examined in patients with hypertension or congestive heart failure. Cody et al[34,35] reported that the single- and multiple-dose pharmacokinetics of captopril in patients with chronic congestive heart failure were not substantially different from those observed in normal subjects (Figure 6). They observed no accumulation of either captopril or its metabolites after daily doses of 25 mg. Richer et al[36] evaluated the single-dose pharmacokinetics of captopril in hypertensive patients and reported data that were consistent with values that have been reported for normal subjects. In another study of patients with hypertension or congestive heart failure, Schwartz et al[37] reported several abnormalities in both groups, including increased AUC disproportionate to dose increases. In the patients with congestive heart failure, clearance of both enalapril and enalaprilat was significantly reduced relative to that in patients with hypertension. The pharmacokinetics of quinapril have also been examined in patients with chronic hypertension.[14] The data from these patients corresponded closely with those from normal subjects. It should be noted that the antihypertensive activity of the drug, however, correlates poorly with plasma ACE inhibition. A much better relation is apparent between the blood pressure-lowering effect of quinapril and aortic ACE inhibition, suggesting that vascular tissue ACE inhibition may be more impor-

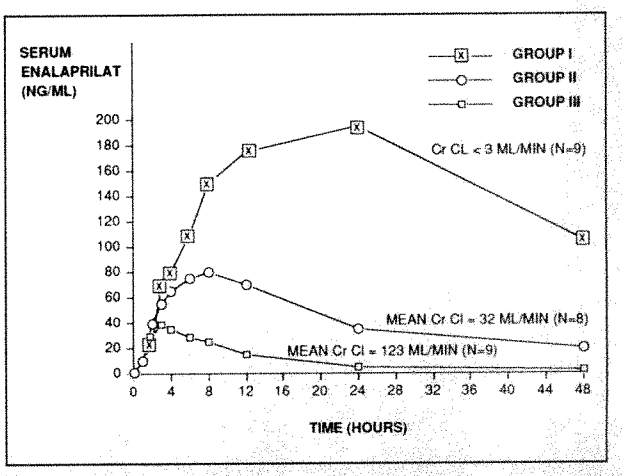


FIGURE 5. Mean serum profiles of enalaprilat in patients with renal insufficiency (groups I and II) and in normal subjects (group III). CrCl = creatinine clearance. (From Lowenthal et al.[28])

tant than plasma ACE inhibition in the antihypertensive effect and overall clinical profile of this drug.

EFFECTS OF FOOD INTAKE AND DRUG–DRUG INTERACTIONS

Intake of food at the time of drug administration can slow absorption and thus change the pharmacokinetic profile of the agent under study. This issue has been examined for these 3 ACE inhibitors. Öhman et al[38] and Muller et al[39] evaluated the effects of food intake on the pharmacokinetics of captopril. Öhman reported that peak plasma concentration and AUC of total and non–protein-bound captopril were slightly but significantly reduced by concomitant food intake (Figure 7). Muller noted that both C_{max} and AUC from 0 to 120 hours (AUC_{0-120}) were reduced when food was ingested at the time of captopril administration. Swanson et al[17] observed no changes in any of the pharmacokinetic parameters for enalaprilat when enalapril was administered in either the fed or fasted states. Ferry et al[21] administered 40 mg oral doses of quinapril to healthy volunteers who were either fasting or had consumed a standard breakfast. There were no significant differences between the 2 treatment groups with respect to either C_{max} or $AUC_{0-\infty}$, but T_{max} for both quinapril and quinaprilat increased significantly in the patients who had eaten breakfast before quinapril administration. Thus, food intake appears to slow the absorption of quinapril but does not change the bioavailability of either quinapril or quinaprilat.

Patients being treated for hypertension are often taking a number of medications concurrently, and potentially dangerous, unexpected, adverse reactions can occur because of changes in the pharmacokinetics of 1 drug induced by the co-administration of another. Drug–drug interactions for captopril, enalapril, and quinapril have been tested extensively.

Drug–drug interactions involving captopril were reviewed recently.[8,40] There are no interactions between captopril and hydrochlorothiazide, furosemide, procainamide, cimetidine, or allopurinol. Drugs that contain either aluminum or magnesium salts significantly reduce the bioavailability of captopril. Concomitant administration of indomethacin markedly reduces the antihypertensive action of captopril, especially in patients with low renin activity. Captopril increases trough plasma concentrations of digoxin in patients with congestive heart failure but not in healthy subjects.

Belz et al[41] reviewed currently available data on drug–drug interactions involving enalapril. They noted that co-administration of enalapril and furosemide did not alter the pharmacokinetic profiles of either agent. Cimetidine, the H_2-receptor antagonist commonly prescribed for the treatment of peptic ulcers, reduces gastric acid secretion and might thus alter the absorption of acid-labile drugs. Cimetidine also inhibits cytochrome P-450 microsomal oxidation and reduces hepatic blood flow. It might, therefore, be expected to alter the hydrolysis of ACE inhibitors such as enalapril and quinapril. Nevertheless, Ishizaki et al[19] have reported that co-ad-

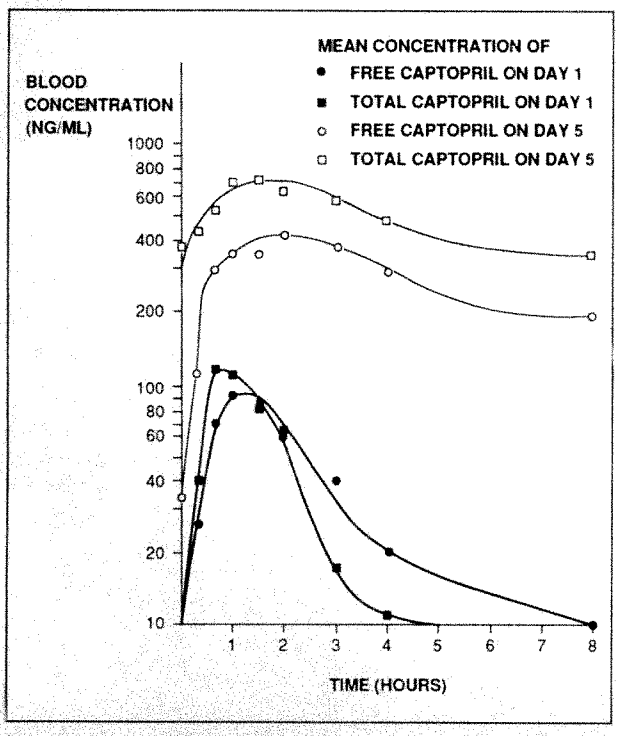


FIGURE 6. Mean concentrations of free and total captopril on days 1 and 5 (n = 12 patients). Except for the difference between free captopril concentrations at 0.67 hour, there is no significant difference between days 1 and 5. (From Cody et al.[35])

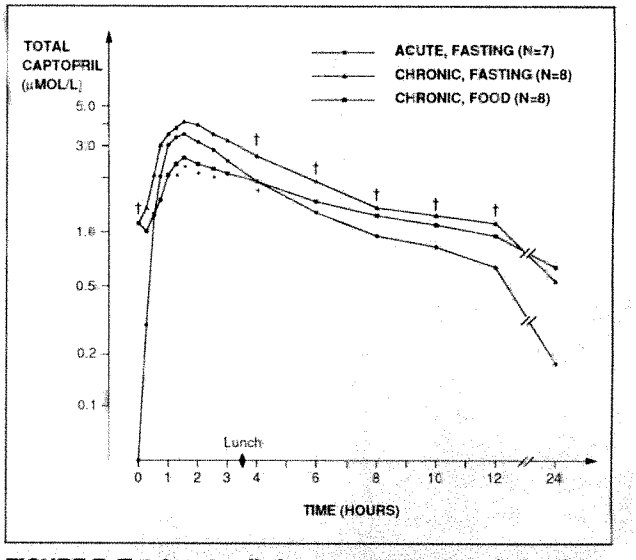


FIGURE 7. Total captopril plasma concentrations during 24 hours after oral intake of 25 mg captopril acute and fasting, after long-term treatment and fasting, and after long-term treatment with concomitant food intake. Standard deviation limits have been omitted for clarity. *p <0.05 chronic study, food versus fasting; †p >0.05 fasting study, acute versus chronic. (From Ohman et al.[38])

ministration of cimetidine and enalapril does not alter the pharmacokinetic parameters of either this ACE inhibitor or its active metabolite.

In the studies carried out to date, there have been no reports of significant drug–drug interactions involving quinapril. Horvath et al[42] administered quinapril alone, hydrochlorothiazide alone, or the 2 drugs in combination to healthy volunteers and reported no significant effect on the pharmacokinetics of either quinaprilat or hydrochlorothiazide. Horvath et al[43] also evaluated whether the β-receptor antagonist propranolol interacts with quinapril in normal subjects. Again, co-administration of the 2 drugs produced no significant changes in the pharmacokinetics of quinaprilat. The effects of cimetidine on the pharmacokinetic profiles of quinapril and quinaprilat have been tested by Ferry et al.[44] No significant differences were reported in pharmacokinetic parameters when quinapril was administered alone or after multiple dosing with cimetidine.

CONCLUSION

While the mechanisms of action of captopril, enalapril and quinapril are essentially the same, the metabolism and pharmacokinetics of captopril are very different from those of the latter 2 agents. Captopril undergoes complex biotransformations in plasma whereas both enalapril and quinapril each have only a single active metabolite that arises from de-esterification in the liver of the parent drug. The fact that captopril has a number of metabolites whereas enalapril and quinapril each have 1 major metabolite makes the elimination kinetics of captopril and its by-products more complex than those for enalapril/enalaprilat and quinapril/quinaprilat.

One apparent difference between quinapril and the other 2 ACE inhibitors considered in this review is that multiple-dose studies have demonstrated no significant accumulation of quinapril. In contrast, several investigators have shown that both captopril and enalapril may accumulate with repeated dosing. It would thus appear that quinapril has the most favorable pharmacokinetic profile for long-term therapy.

Since all of these agents and their metabolites are eliminated primarily via renal excretion, renal impairment is a predictable precursor of reduced clearance and thus accumulation of the drug. Indeed, numerous studies have demonstrated that renal insufficiency, regardless of its causes, reduces clearance and increases AUC for all of these agents. Demonstrations that hepatic insufficiency reduces enalaprilat and quinaprilat AUCs confirm that enalapril and quinapril are converted to their active metabolites in the liver.

The ACE inhibitors reviewed in this report rarely interact with other agents used to treat hypertension or congestive heart failure. The effect of captopril on trough serum concentrations of digoxin is a potentially serious drug–drug reaction, however. When captopril and digoxin are administered together, increased serum concentrations of digoxin might possibly lead to digoxin intoxication. Accordingly, digoxin serum concentrations should be monitored carefully in patients who are also receiving captopril.

An important caveat with respect to the pharmacokinetic studies reviewed in this report should be noted. Knowledge of pharmacokinetic parameters and correlation of blood or plasma drug concentrations with both hemodynamic actions and adverse reactions permits prediction of effective drug doses only if the correlations between drug levels and hemodynamic actions are strong. There is some evidence that plasma levels of ACE inhibitors may not be highly correlated with their hemodynamic actions. The model proposed by Belz et al,[41] in

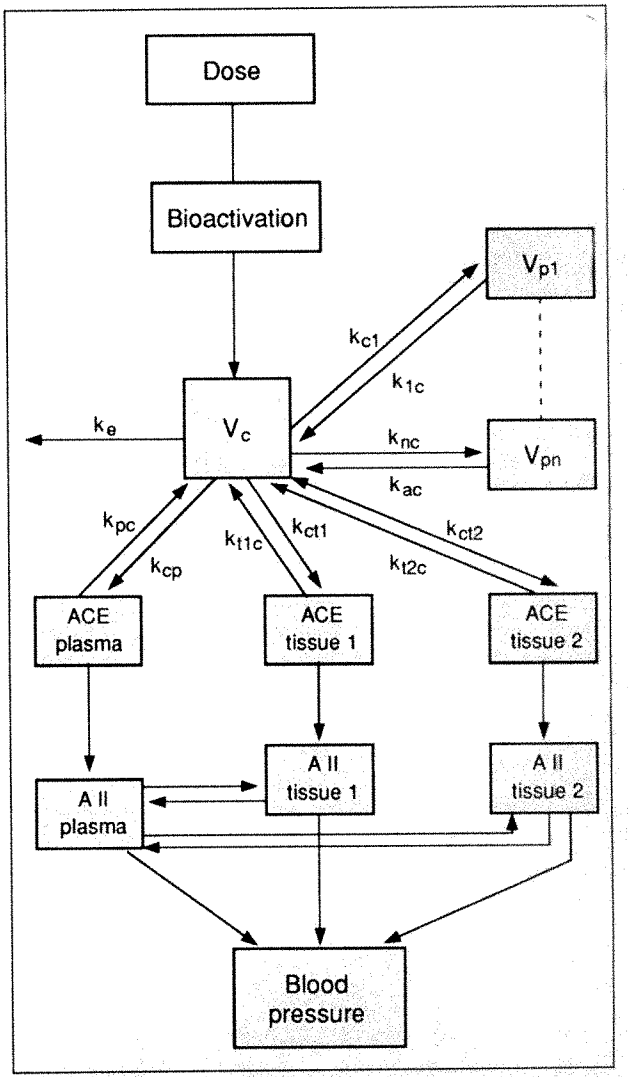


FIGURE 8. Pharmacokinetic/pharmacodynamic model for angiotensin-converting enzyme (ACE) inhibitors. After absorption and bioactivation, the drug is distributed in the plasma compartment (V_c). From here it readily penetrates into peripheral compartments (V_{p1} to V_{pn}) and binds to ACE. As a result of this binding, angiotensin II levels and blood pressure are reduced. (From Belz et al.[41])

fact, suggests that concentrations of ACE inhibitors in local tissues rather than in plasma may be more directly related to their actions on blood pressure (Figure 8). In this regard, it is interesting to note that animal experiments carried out by Kaplan et al[7] have shown that quinapril levels in aortic tissue have a better correlation with blood pressure reduction than do plasma concentrations of the drug. Nevertheless, the metabolism and pharmacokinetic parameters of all 3 ACE inhibitors indicate that they are suitable for use in a wide range of patients. This fact, when combined with their high degree of clinical efficacy, has firmly established ACE inhibitors in the treatment of both hypertension and heart failure.[45]

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Comparative Pharmacokinetic and Clinical Profiles of Angiotensin-Converting Enzyme Inhibitors and Calcium Antagonists in Systemic Hypertension

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Angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists are important classes of antihypertensive agents. Within their respective classes, ACE inhibitors and calcium antagonists share common pharmacokinetic properties, but in contrast to ACE inhibitors, some calcium antagonists may cause a significant increase in plasma digoxin concentrations. Clinically, both classes of agents have been shown to be safe and effective in large-scale, long-term clinical trials. ACE inhibitors appear to be very well tolerated and may be associated with fewer adverse effects than some calcium antagonists. ACE inhibitors appear to blunt diuretic-induced hypokalemia, hypercholesterolemia, hyperuricemia, and hyperglycemia. Both classes of agents can be used safely in patients with renal disease, diabetes mellitus, peripheral vascular disease, and chronic obstructive pulmonary disease. They may also be used in the elderly. While ACE inhibitors are particularly useful in hypertension accompanied by congestive heart failure, calcium antagonists can be very useful when angina pectoris is present in the hypertensive patient.

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Angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists are important new classes of antihypertensive agents. The 1988 Joint National Committee report[1] included ACE inhibitors and calcium antagonists as well as β-adrenergic blocking agents and diuretics as possible first-step therapy for hypertension. ACE inhibitors and calcium antagonists may have fewer side effects than diuretics or β blockers in given individuals, enabling physicians to tailor their treatment of hypertension. ACE inhibitors and calcium antagonists have been shown to control mild hypertension in about 50–60% of patients, and when used in combination may control hypertension in 85–90% of patients.

Seven orally active ACE inhibitors—benazapril, captopril, enalapril, fosinapril, lisinopril, quinapril, and ramipril—and 8 orally active calcium antagonists—amlodipine, bepridil, diltiazem, felodipine, nicardipine, nifedipine, nimodipine, and verapamil—are currently available for clinical use in the United States, although their approved indications vary. Other agents in both classes are currently under review. We review their comparative pharmacokinetics and clinical profiles, and discuss the potential advantages and disadvantages of each group of antihypertensive drug.

COMPARATIVE PHARMACOKINETICS

Angiotensin-converting enzyme inhibitors: It has been established that increased levels of angiotensin II, a potent vasoconstrictor found in vascular and other tissues, may be partly responsible for hypertension. ACE inhibitors decrease systemic blood pressure by inhibiting the formation of angiotensin II not only in the peripheral circulation but also at the tissue level.[2,3] Captopril was the first ACE inhibitor approved for use in patients with hypertension or congestive heart failure. Because early experience with high doses of captopril was associated with significant side effects similar to those of other drugs containing mercapto groups (e.g., penicillamine), other ACE inhibitors without sulfhydryl groups were developed. Among these are enalapril (MK421), lisinopril, and quinapril (Figure 1).

The ACE inhibitors share certain pharmacokinetic properties, including rapid absorption from the gastroin-

TABLE I Pharmacokinetics of some ACE Inhibitors

	Captopril	Enalapril	Lisinopril	Quinapril
Oral absorption (%)	60–75	60–70	25	60
Bioavailability (%)	62	40	25	30
Protein binding (%)	25–30	<50	none	97
Elimination				
Metabolism	renal	renal	renal	renal
Urinary excretion of unchanged drug (%)	40–50	61	97	61
Active metabolites	yes	yes	no	yes
Half-life* (hours)	1.7	11†	12.6†	1

* Half-life may be increased in patients with renal failure, necessitating an adjustment of dose.
† Accumulation half-life.
ACE = angiotensin-converting enzyme.

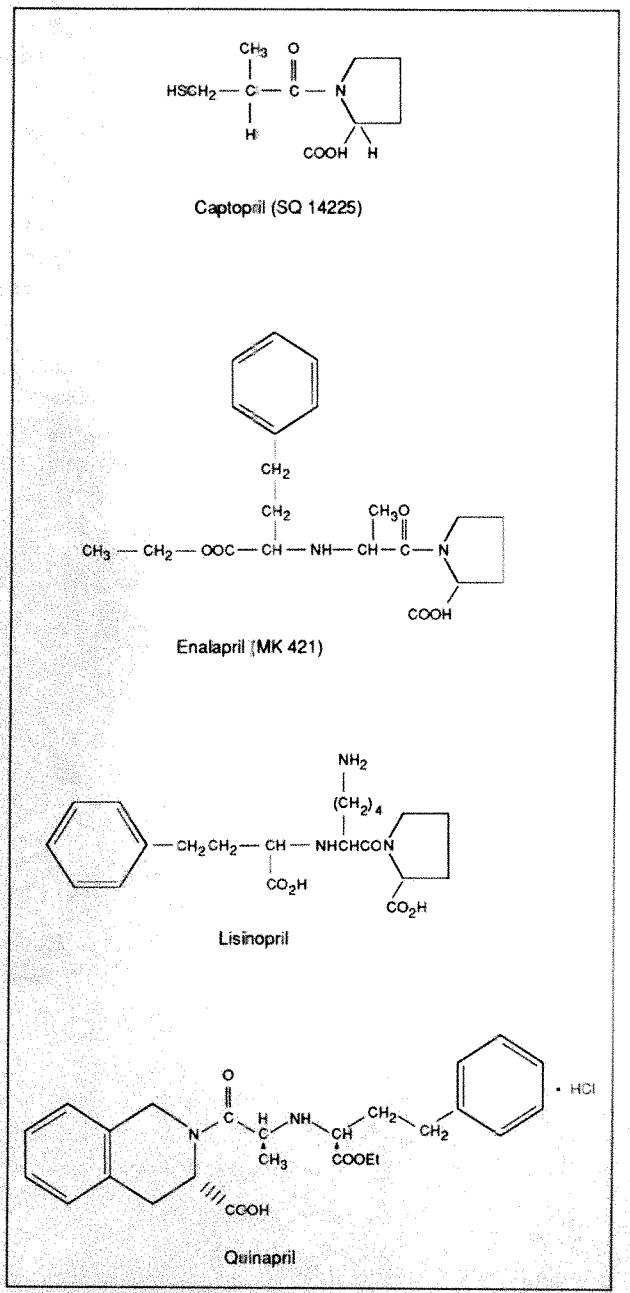


FIGURE 1. Chemical structures of some of the angiotensin-converting enzyme inhibitors.

testinal tract, wide distribution to most tissues in the body, and renal excretion. The pharmacokinetics of this class of agents in patients with uncomplicated hypertension are the same as in healthy subjects. However, because all four ACE inhibitors are excreted by the kidney, one would expect differences in patients with secondary renal dysfunction.[4] The specific pharmacokinetic properties of each agent are described below and are listed in Table I.

Captopril: Detectable plasma concentrations of captopril are apparent as early as 15 minutes after oral administration. The extent of absorption is approximately 60–75% of an oral dose,[5] and peak plasma concentrations occur after approximately 1 hour.[6] The presence of food in the gastrointestinal tract reduces the absorption of captopril by as much as 30–40%.[7] Although captopril is 25–30% protein bound in blood, it is widely distributed to most tissues, with the exception of the central nervous system.[6]

Renal excretion of captopril is rapid, with 90% of unchanged drug excreted in the first 4 hours.[6] The elimination half-life for unchanged captopril is about 1.7 hours in healthy individuals and is markedly increased in the presence of renal insufficiency. Elimination half-life correlates closely with endogenous creatinine clearance,[6,8] and patients with renal insufficiency have much higher peak plasma concentrations than patients with normal renal function.

Enalapril: The extent of absorption of enalapril is 60–70% of an oral dose.[6] Unlike captopril, the presence of food in the gastrointestinal tract does not appear to influence its absorption.[9]

Once absorbed, enalapril is rapidly metabolized to its active form, enalaprilat, which appears to be its only metabolite. Therefore, intact enalapril is found in the serum for only a very short period and is almost undetectable 4 hours after oral administration.[6] The de-esterification of enalapril to enalaprilat probably occurs in the liver by hepatic esterases.[6]

After oral administration of enalapril, the time of maximum observed plasma concentration (T_{max}) for enalapril is 1 hour and that for enalaprilat is 4 hours. The half-life of enalaprilat after chronic administration of enalapril is 11 hours; however, in many individuals the duration of antihypertensive activity is 24 hours. Thus, enalapril has a much longer duration of action than captopril.

Lisinopril: Lisinopril, a lysine analog of enalaprilat, is absorbed intact after oral dosing, with peak serum concentrations occurring within approximately 6 hours.[10] The average bioavailability of lisinopril is 25%, and it is not significantly affected by the presence of food in the gastrointestinal tract.

Lisinopril is neither metabolized nor protein bound.[10] Steady-state serum concentrations are achieved in 2–3

TABLE II Pharmacokinetics of some Calcium Antagonists

	Diltiazem	Verapamil	Nifedipine	Nicardipine
Oral absorption (%)	90	90	90	90–100
Bioavailability (%)	40–50	10–20	40–50	35
Protein binding (%)	70–80	90	90	95
Elimination				
Metabolism	hepatic (50% first-pass metabolism)	hepatic (79% first-pass metabolism)	hepatic	hepatic (99% first-pass metabolism)
Urinary excretion of unchanged drug (%)	0.1–4	>5	trace	<1
Active metabolites	yes	yes	no	no
Half-life* (hours)	3–5	3–7	2–5	2–4

* Half-life may be increased in cirrhosis and multiple dosing, necessitating a decrease in dose.

days, with little accumulation. The effective accumulation half-life after multiple dosing is 12 hours.[11] Significant accumulation occurs in patients with severe renal impairment (creatinine clearance <30 mL/min).[10]

Quinapril: Pharmacokinetic studies in animals show that once absorbed, quinapril is converted to quinaprilat, the pharmacologically active metabolite.[12,13] Quinapril absorption and hydrolysis to quinaprilat is rapid, with peak quinapril and quinaprilat concentrations occurring 1–2 hours after the dose. Similar to enalapril and lisinopril, absorption of quinapril and conversion to quinaprilat is not affected by the presence of food in the gastrointestinal tract.[14]

Metabolism to compounds other than quinaprilat is not extensive. Plasma profiles for these metabolites indicate rapid elimination, with no potential for accumulation after the recommended once- or twice-daily dosing.[13] The half-life of quinapril and quinaprilat is approximately 1 hour.[13] In patients with renal insufficiency, clearance of quinaprilat is reduced in direct proportion to declining renal function as assessed by creatinine clearance.[15] It has been shown, however, in a study with [^{14}C]quinapril, that 37% of the dose ingested by healthy volunteers was excreted in the feces.[4] This demonstrates a biliary route of quinapril excretion in addition to the renal route, and a possible mechanism for the prevention of buildup of quinapril in blood. The effects of quinapril (20 mg once daily on day 1 and again on days 4 through 10) on renal function parameters were tested in a study of 22 patients, of whom 17 completed the trial and were assessed.[4] Patients were stratified according to creatinine clearance rates, with 4 having a rate ≥60 mL/min, 5 with creatinine clearance rates in the range of 30–59 mL/min, and 8 with creatinine clearance rates <30 mL/min. Quinapril had no effect on creatinine clearance in any of these groups. In a further study of 20 patients, neither creatinine nor urea concentrations in serum were altered by once-daily dosing with quinapril for 7 consecutive days.[4]

Calcium antagonists: The therapeutic actions of calcium antagonists arise from their ability to inhibit the influx of calcium ions across the plasma membranes of excitable cells, resulting in a physiologic relaxation of resistance vessels.[16] Five calcium antagonists—verapamil, diltiazem, nifedipine, nicardipine, and nimodipine—are now approved for clinical use.

Despite their very different chemical structures (Figure 2), verapamil, diltiazem, and nifedipine share common pharmacokinetic properties (Table II). These include extensive first-pass hepatic extraction after oral administration, high clearance, with total metabolic clearance 50–75% of hepatic blood flow, and extensive binding to plasma proteins. Such high clearance results in low bioavailabilities (diltiazem, 40–50%; nifedipine, 40–50%; verapamil, 10–30%) despite almost complete absorption after oral administration and elimination half-lives of 2–7 hours. Thus, multiple daily doses are required to achieve steady-state plasma concentrations

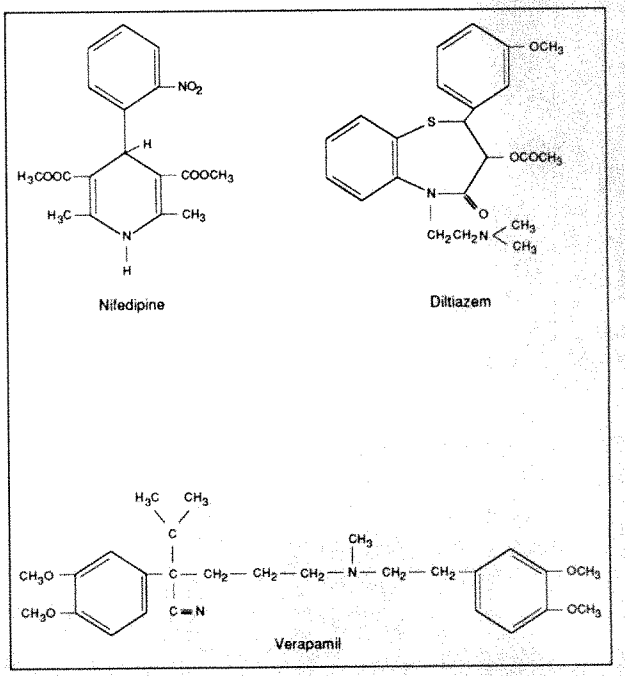


FIGURE 2. Chemical structures of some of the calcium antagonists.

with acceptable interdose fluctuation.[17] New products with a longer half-life or sustained-release vehicles have obviated this requirement.

Renal disease has no impact on the pharmacokinetics of diltiazem and verapamil. However, the elimination half-life of nifedipine increases in relation to the degree of renal impairment due to increased volume of distribution. Systemic clearance remains unchanged.[17] In contrast, the pharmacokinetics of calcium antagonists are greatly altered in patients with liver cirrhosis. Clearance decreases, elimination half-life is substantially prolonged, and bioavailability more than doubles. In addition, the volume of distribution increases.[17]

Drug interactions: ACE inhibitors can be combined with many other antihypertensive agents without producing unfavorable side effects. Of particular clinical importance is the lack of clinically meaningful pharmacokinetic interactions between ACE inhibitors and digoxin.[18] In contrast, concomitant administration of calcium antagonists with digoxin should be done with caution. Both verapamil and diltiazem may cause a significant increase in plasma digoxin concentrations, which may increase to toxic levels.[17,18] The mechanism responsible for this interaction is believed to be inhibition of both renal and non-renal digoxin clearance.[17] This effect does not appear to occur with nifedipine. Co-administration of calcium antagonists and β blockers may be hazardous since the negative inotropic and chronotropic effects of the drugs may be additive, and may result in serious conduction and rhythm disturbances as well as significant impairment of left ventricular function.[17] No unfavorable interactions between ACE inhibitors and β blockers have been reported thus far.[19]

CLINICAL PROFILES OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND CALCIUM ANTAGONISTS

Comparative efficacy as monotherapy: Both ACE inhibitors and calcium antagonists are now included as first-step therapy for the treatment of hypertension, and both are safe and effective. No single antihypertensive agent should be expected to normalize blood pressure in all patients. When given as monotherapy, ACE inhibitors can be expected to normalize blood pressure in approximately 60% of all hypertensive patients,[19] although a recent report suggests that quinapril is effective as monotherapy in a larger percentage of elderly hypertensive patients.[20] With concomitant sodium depletion induced by diet or the administration of diuretics, blood pressure normalization can be achieved in >90% of patients.[19] Similarly, monotherapy with calcium antagonists has been found to normalize blood pressure in approximately 50–60% of an unselected group of patients with mild to moderate hypertension. Both classes of agents have been shown to be effective in the elderly.[21,22]

ACE inhibitors appear to be well tolerated and may be associated with fewer side effects and an improved quality of life.[23,24] Their addition to the conventional therapeutic regimen in patients with severe cardiac failure may reduce mortality.[25] Additionally, data suggest that ACE inhibitors may exert a beneficial action on the kidney. Patients with essential hypertension have been shown to have a greater renal blood flow response and, despite the decrease in arterial blood pressure, well-maintained glomerular filtration rate.[26]

Calcium antagonists have been reported to be most effective in patients with low renin levels (e.g., some elderly and black patients).[21] However, the correlations between blood pressure response and plasma renin may have little predictive value for individual patients. Calcium antagonists also appear to protect the renal vasculature from the smooth muscle mitogenic effects of angiotensin II and norepinephrine, and may limit development of intraglomerular hypertension and minimize the chances for hypertensive nephrosclerosis to develop.[27,28]

Comparative efficacy as combination therapy: If monotherapy with an ACE inhibitor or a calcium antagonist fails to control blood pressure sufficiently, they can each be combined with a number of other agents with different mechanisms of action. ACE inhibitors can be safely combined with diuretics, β blockers, or calcium antagonists. Combination therapy with an ACE inhibitor and a low-dose thiazide diuretic enhances the antihypertensive effect of both drugs and also reduces some of the adverse effects associated with the diuretic. Specifically, diuretic-induced hypokalemia, hyperuricemia, hyperglycemia, and hypercholesterolemia can be blunted by concurrent use of an ACE inhibitor.[19] Since hypokalemia is uncommon with the combination of an ACE inhibitor and a diuretic, the use of potassium supplements or potassium-sparing agents is generally not required. It should be noted that excessive use of diuretics can produce severe hypotension and deterioration of renal function.

ACE inhibitors have also been used safely with concomitant administration of β blockers. Some investigators have reported improved blood pressure control with ACE inhibitors and β blockers. Others, however, have found that the combination of these 2 classes of drugs appears to increase the antihypertensive effects of both drugs only slightly.[19]

The combination of ACE inhibitors and calcium antagonists also provides additive antihypertensive effects.[19] Results of a study of the additive effect of isradipine in combination with captopril indicated that combined treatment with a calcium antagonist and ACE

nhibitor is effective in lowering blood pressure and that he combination is well tolerated during long-term thera-)y (24 weeks).[29] Combination therapy consisting of cal-:ium antagonists and ACE inhibitors has also been re-)orted to be an effective treatment in severe hyperten-sion.[30,31]

In addition to ACE inhibitors, calcium antagonists nave been used in combination with diuretics, β blockers, and α blockers. While calcium antagonists can be used safely with diuretics, concomitant therapy with a diuretic and calcium antagonist has had variable effects on blood pressure control.[32] However, a recent double-blind cross-over comparison of nitrendipine and hydrochlorothiazide in 87 patients found that the 2 agents had additive effects on blood pressure over 8-week periods.[32]

In most studies, the addition of a β blocker to a calcium antagonist has resulted in positive effects on blood pressure control.[33] However, caution should be used when combining verapamil or diltiazem with β-blocker treatment, since this combination may induce severe sinus bradycardia, increase heart block, or precipitate heart failure.

Concomitant administration of calcium antagonists and α blockers potentiates the antihypertensive effects of the α blocker and may be of therapeutic value.[32] It is important to note that any combination approach should be done cautiously, as profound hypotension may result.

SPECIFIC PATIENT POPULATIONS

The elderly: The physiologic changes that occur with aging can alter the kinetics of many drugs in the elderly, mainly because of decreased elimination rate or alteration in drug distribution. Elderly patients are particularly prone to develop side effects with some of the most frequently used antihypertensive drugs. ACE inhibitors and calcium antagonists have been shown to be effective and well tolerated in the elderly, providing a logical alternative to traditional therapy.

The ACE inhibitors are especially attractive in the elderly due to their low incidence of adverse effects and potentially positive impact on the patient's quality of life.[24] Captopril has been studied in >1,000 elderly patients with mild to moderate hypertension and has been shown to be effective in this population. Low doses of captopril (<150 mg/day) with or without low doses of a diuretic were effective in normalizing blood pressure.[34,35]

Similar experiences have been reported with enalapril,[19] lisinopril,[36] and quinapril.[21] For example, Frank et al[20] found that once-daily quinapril (20 or 40 mg) effectively reduced baseline diastolic blood pressure in elderly hypertensive patients with a mean measurement of 104.8 mm Hg. Peak mean reductions in diastolic pressure (both doses combined) of 13.9 and 17.3 mm Hg were seen at 3 and 2 hours after the dose on days 1 and 28, respectively. On both days, maximum plasma concentrations of quinapril and quinaprilat occurred within 2 hours after the dose. When these plasma concentrations were compared with blood pressure reductions at individual time points, however, no correlation was found. There was no evidence of a "first-dose" effect, and the mean peak reduction in blood pressure after the first dose of quinapril tended to be greater with the 20-mg rather than the 40-mg dose, suggesting that the magnitude of blood pressure reduction after the first dose is not related to dose. Moreover, quinapril has not been associated with an increased incidence of adverse events in the elderly population.[36]

Despite the age-related reduction in renal blood flow and glomerular filtration rate, renal function is usually preserved during ACE inhibition, and even patients with elevated serum creatinine levels have had no reduction in renal function.[19,36] However, these agents should be used cautiously with frequent electrolyte and renal function determinations as clinically indicated. It is important to note that in the elderly, blood urea nitrogen and creatinine may not be accurate reflections of renal function. The tendency toward accumulation of this class of drug appears to occur only in patients with more severe renal impairment.[36] In addition, the lack of a precipitous reduction in blood pressure with ACE inhibitors[36] is of particular relevance to the elderly, in whom baroreflex function is less efficient[34] and orthostatic problems are common.

ACE inhibitors are especially useful in elderly patients with multiple concomitant medical illnesses, such as diabetes mellitus, hypercholesterolemia, and peripheral vascular disease; these agents do not adversely affect these conditions, and in some cases may be beneficial. Moreover, in both normotensive and hypertensive patients with congestive heart failure, ACE inhibitors reduce afterload and improve cardiac output and exercise tolerance while reducing congestive symptoms.

Calcium antagonists are also suitable for treatment of elderly hypertensive patients. Similar to ACE inhibitors, calcium antagonists do not induce biochemical abnormalities, central nervous system dysfunction, postural hypotension, or salt or water retention. However, constipation may be a problem in elderly patients receiving calcium antagonists, particularly verapamil, and bowel habits should be carefully monitered.

Of the currently available calcium antagonists, nifedipine is the most potent vasodilator. Nifedipine can rapidly lower blood pressure in most patients. In 1 study of calcium antagonists in the management of hypertension in the elderly,[37] nifedipine (20 mg twice daily) adequately controlled blood pressure in 71% of 21 elderly (mean

TABLE III Use of ACE Inhibitors or Calcium Antagonists in Patients With Concomitant Diseases

ACE Inhibitors
Favor in patients with
Congestive heart failure; diabetes mellitus; diabetic nephropathy; peripheral vascular disease; hypercholesterolemia; chronic obstructive pulmonary disease; asthma; adverse reactions to other drugs.
Use with caution in patients with
Renal failure (except diabetic); renal artery stenosis; volume depletion.
Calcium Antagonists
Favor in black patients and patients with
angina pectoris; supraventricular tachycardia (verapamil); vascular disease; hypercholesterolemia; chronic obstructive pulmonary disease; asthma; chronic renal failure.
Use with caution in patients with
sick sinus syndrome; atrioventricular block; congestive heart failure.

ACE = angiotensin-converting enzyme.

age 79 ± 2 years) hypertensive patients. Other reports also indicate that nifedipine and verapamil provide effective monotherapy in elderly patients.[37,38]

Calcium antagonists can be used safely in patients with diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, and chronic renal failure (Table III). They are especially useful for the treatment of angina pectoris or, in the case of intravenous verapamil, supraventricular dysrhythmias. However, verapamil and diltiazem may aggravate underlying conduction disturbances. Therefore, these agents should be avoided in patients with sick-sinus syndrome, atrioventricular block, or congestive heart failure.[37] As previously mentioned, some calcium antagonists should not be used concomitantly with β blockers. Also, digoxin should be used cautiously in patients receiving either verapamil or diltiazem.

Diabetics: Hypertension is approximately twice as common in diabetic as in nondiabetic patients.[39] Treatment of hypertension in this patient population is particularly important since high blood pressure "hastens" the progression of diabetes mellitus, whereas reduction in blood pressure may slow the progression of diabetic nephropathy.[39] Moreover, diabetic patients who develop hypertension may be particularly vulnerable to renal injury that is probably caused by underlying abnormalities of the renal circulation induced by diabetes.

Treatment of essential hypertension in diabetic patients differs somewhat from the usual treatment, since metabolic and other side effects of antihypertensive agents can be particularly harmful in these patients. Most diabetic patients can receive an ACE inhibitor or a calcium antagonist as initial therapy, and both may have advantages over thiazide diuretics and β blockers as a first-line therapy in this patient population.[39] Importantly, administration of these agents does not alter insulin secretion and has little or no effect on control of diabetes mellitus. In addition, neither class of agents aggravates lipid abnormalities, and impotence is rare. If fluid retention is a problem, concomitant use of diuretics may be needed.

ACE inhibitors are an especially attractive choice in hypertensive diabetic patients with nephropathy. Preliminary data suggest that these drugs reduce proteinuria and albuminuria and preserve renal function by reducing intraglomerular blood pressure.[40,41] Reduction in glomerular capillary pressures was not reproduced by other agents.[42] This is especially important in diabetic patients, who are particularly vulnerable to renal injury due to underlying abnormalities of the renal circulation induced by diabetes. Although hyperkalemia did not present a problem in these studies, the potential exists, and serum potassium and creatinine levels should be monitored in patients with diabetic nephropathy receiving an ACE inhibitor.

Blacks: Black patients with hypertension have markedly elevated vascular resistance and a tendency for development of cardiovascular disease. Therefore, they need antihypertensive agents that lower blood pressure and total peripheral resistance, while maintaining tissue perfusion. As in all hypertensive patients, blood pressure should be controlled at a local vascular level in the kidney, brain, heart, and other vascular beds in a physiologic way so as to maintain function and perfusion.

In addition to decreasing systemic blood pressure, ACE inhibitors can reduce intraglomerular pressure, increase renal blood flow, cause regression of left ventricular hypertrophy and ventricular ectopy, and potentially reduce the risk of coronary artery disease as well as congestive heart failure.[27,41,43] These characteristics make the ACE inhibitors capable of reducing some of the major cardiovascular complications of hypertension, which is especially important in black hypertensive patients, who are predisposed to early and accelerated cardiovascular disease.[27]

Nevertheless, some black patients appear less responsive to monotherapy with ACE inhibitors than nonblacks because of their low-renin, salt-sensitive profile.[27] Therefore, ACE inhibitors may be most effective in the black hypertensive patient when combined with thiazide diuretics. They are also particularly suited to patients who have symptoms of congestive heart failure or conduction system disease in which other agents such as β blockers or calcium antagonists would be relatively contraindicated. Black patients tended to have a better response with the new ACE inhibitor quinapril than with captopril.[44]

Calcium antagonists are also useful in the black population, especially in those blacks who tend to have lower renin levels. Similar to ACE inhibitors, calcium antago-

nists reduce vascular resistance, improve left ventricular function through afterload reduction, and improve renal blood flow, which may explain their natriuretic effect. Thus, they are well suited to treat the high vascular resistance, reduced renal blood flow, mildly reduced cardiac output, and expanded plasma volume seen in the black hypertensive patient.

Congestive heart failure: ACE inhibitors are probably the drugs of choice in hypertensive patients with associated congestive heart failure, since they are known to improve both disorders without the development of tolerance.[19] In contrast, calcium antagonists may exacerbate congestive heart failure due to the negative inotropic action of these drugs.[32]

Renal disease: Hypertension resulting from reduction in renal blood flow due to renal artery stenosis represents the most common curable form of secondary hypertension, and is still believed by many investigators to contribute to the pathogenesis of essential hypertension in some patients. Both ACE inhibitors and calcium antagonists have a place in the therapy of hypertensive patients with renal disease.

ACE inhibitors are quite effective in hypertensive patients with renal failure.[45] These drugs, given alone or in combination with a diuretic, have been shown to increase renal blood flow and improve glomerular filtration rate in patients with impaired renal function.[46] However, the dose of the drug must be adjusted to renal function, since all ACE inhibitors currently available are excreted by the kidney. Since it is known that the renin–angiotensin system is involved in the pathogenesis of hypertension due to renal artery stenosis, it is not unexpected that ACE inhibitors control hypertension in a majority of such cases.

However, whereas ACE inhibitors usually cause a marked blood pressure decrease in patients with renovascular hypertension, they have been reported to cause acute renal impairment in patients with bilateral renal artery stenosis or stenosis in the artery supplying a solitary kidney.[47] Since renal perfusion pressure behind the stenosis may become very low and no angiotensin II is available to maintain postglomerular resistance, there is often a decrease or even a cessation of glomerular filtration in the stenotic kidney.[47] Therefore, long-term treatment of renovascular hypertension with ACE inhibitors should be avoided unless alternative therapy, mostly correction of the stenosis, is not available or possible.

Calcium antagonists can be used safely in patients with chronic renal failure or renal artery stenosis. These agents increase renal plasma flow, maintain glomerular filtration rate, and cause brisk diuresis and natriuresis.[27] Verapamil attenuates the intrarenal effects of angiotensin II and norepinephrine and has no short-term or long-term effects on renal function.[27,48]

Respiratory disease: Both ACE inhibitors and calcium antagonists have been shown to be effective in hypertensive patients with accompanying respiratory disease. When ACE inhibitors were used for a period of 2 months to treat hypertensive patients suffering from chronic obstructive pulmonary disease, there was a significant reduction in systolic and diastolic blood pressure, as well as an increase in vital capacity.[19] Importantly, no significant change in the other respiratory function tests and no side effect such as bronchospasm occurred. ACE inhibitors were also found to be safe in the treatment of hypertensive patients with asthma.[49]

Similarly, calcium antagonists do not negatively influence airway resistance in patients with chronic obstructive lung disease or bronchial asthma even after histamine challenge.[32] Thus, they too can be safely given to patients with obstructive pulmonary disease or asthma.

COMPARATIVE SAFETY AND SIDE EFFECTS

ACE inhibitors and calcium antagonists are as safe as the "older" agents available for treatment of hypertension. In comparison with β blockers and diuretics, ACE inhibitors and calcium antagonists have relatively mild metabolic effects. They have essentially no effect on serum potassium, glucose, uric acid, cholesterol, or triglycerides. In addition, neither ACE inhibitors nor calcium antagonists cause bronchoconstriction, and as previously discussed, can be very effective in patients with respiratory dysfunction. Recommended doses of ACE inhibitors generally are free of significant cardiotoxicity or adverse central nervous system effects.

Nevertheless, ACE inhibitors and calcium antagonists have been associated with some adverse effects. Of the ACE inhibitors, the newer nonsulfhydryl compounds (i.e., lisinopril, quinapril) have fewer side effects than sulfhydryl compounds (e.g., captopril).[10,19,36] In general, sulfhydryl compounds can induce adverse effects such as rash, taste disturbances, nephropathy, and neutropenia. All of these problems have been seen to some extent with captopril and other sulfhydryl-containing ACE inhibitors. In contrast, ACE inhibitors that do not contain a sulfhydryl group have been associated with lesser incidence of problems.

For example, lisinopril, a nonsulfhydryl ACE inhibitor, does not cause hypokalemia, hyperglycemia, hyperuricemia, or hypercholesterolemia. No cases of drug-related neutropenia were observed in over 2,800 people studied.[10] Taste alterations, proteinuria and rash were rare. Cough, azotemia, and angioedema are class effects; the incidence of these problems noted with lisinopril appears to be no different from that observed with captopril and enalapril. Similar findings have been reported with

quinapril.[51] Moreover, the incidence of adverse events reported with quinapril is less than that with both captopril[44] and enalapril,[50] indicating that quinapril may have a slight safety advantage over the 2 older agents.

Cough is a recently recognized adverse effect of ACE inhibitors.[52] The cough tends to be dry, is associated with a tickling sensation in the throat and occasionally with nasal stuffiness, is not associated with symptoms of asthma, and is probably secondary to the effect of ACE inhibition on bradykinin or prostaglandin production.[52] The incidence is about the same with captopril, enalapril, and lisinopril,[10] and slightly lower (about 1.8%) with quinapril.[51] The cough is mild and rarely requires discontinuation of therapy. Patients with underlying renal insufficiency or with severe hypertension may be more susceptible to the adverse effects of ACE inhibitors than patients with uncomplicated hypertension.

The incidence of adverse effects with some calcium antagonists may be higher than that seen with ACE inhibitors.[34] The most common adverse effects are lightheadness, headache and flushing, ankle and occasional periorbital edema, and a burning sensation in the lower extremities. Constipation is also a problem with verapamil and diltiazem.

The occurrence of edema during treatment with calcium antagonists is not a consequence of renal retention of sodium and water, but the result of transfer of fluid from the plasma compartment to the interstitial space, caused by an increase in capillary hydrostatic pressure due to the relative selectivity of calcium antagonists for the arterial side of the circulation.[32]

Hypertensive patients treated with verapamil and diltiazem generally do not have substantial changes in heart rate despite the vasodilating effects of the drug. However, patients treated with short-acting dihydropyridines such as nifedipine, nitrendipine, or nicardipine may experience reflex tachycardia. All calcium antagonists have negative inotropic effects and should be used with caution in patients with congestive heart failure.

CONCLUSION

ACE inhibitors and calcium antagonists have been shown to be safe and effective in treating all forms of essential hypertension. These agents are also effective in patient populations in whom the more traditional agents have been less effective or contraindicated. The ACE inhibitors and calcium antagonists have few adverse effects and may improve the quality of life in patients. While ACE inhibitors appear to be the agents of choice in patients with congestive heart failure, calcium antagonists and β-adrenergic blocking agents are the best selection in patients with angina pectoris. ACE inhibitors should be avoided in patients with bilateral renal artery stenosis, and calcium antagonists should be avoided in patients with congestive heart failure.

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Comparative Properties of Angiotensin-Converting Enzyme Inhibitors: Relations with Inhibition of Tissue Angiotensin-Converting Enzyme and Potential Clinical Implications

David T. Nash, MD

This review summarizes the evidence indicating that local synthesis of angiotensin II, and interference with this process by inhibition of angiotensin-converting enzyme (ACE), may be important in the treatment of hypertension. Inhibition of tissue converting enzyme generally has a stronger correlation with the hemodynamic effects of ACE inhibitors than inhibition of ACE in plasma. Reported differences in the ability of ACE inhibitors to penetrate tissues and to bind to the converting enzyme may be closely related to the relative lipophilicity of these agents. Finally, correlation of data from clinical studies with results provided by laboratory experimentation suggests that the efficacy of different ACE inhibitors in hypertensive patients may be predicted from differences among the actions of these drugs in vitro and in whole animals.

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The renin–angiotensin system plays a central role in cardiovascular homeostasis and in the etiology of hypertension.[1] Until recently, the renin–angiotensin system was thought to be a circulating endocrine system whose components were secreted by different organs and whose ultimate product, angiotensin II, acted on specific receptors in multiple targets including blood vessels, kidneys, adrenal glands, the brain, anterior pituitary, uterus, and heart.[2]

It is now established that angiotensin II may be synthesized locally in a variety of tissues, and that the local production of this hormone may influence many organs. Considerable evidence also indicates that locally produced angiotensin II may play a role in the regulation of blood pressure.[3,4] Recent studies[2] have shown that the genes for both renin and angiotensinogen are expressed in multiple organs. In addition, cardiac myocytes, cultured vascular smooth muscle cells, and endothelial cells can synthesize renin, angiotensins, and renin substrate.

Locally produced angiotensin II may influence vascular tone through either paracrine or autocrine effects, and might also enhance release of norepinephrine from nerve terminals on blood vessels.[2] Dzau[5] has further proposed that elevated angiotensin II concentrations in tissue may be responsible for long-term hypertension and that local, rather than circulating, angiotensin II is the primary regulator of vascular tone.

Angiotensin-converting enzyme (ACE) inhibiting agents have emerged with diuretics, β-adrenergic blocking agents, and calcium antagonists as a first-line therapeutic option for the initial treatment of hypertensive patients.[6] The actions of these agents have generally been associated with the circulating renin–angiotensin system, but it is likely that they also influence local or tissue production of angiotensin II.

LOCALIZATION OF TISSUE ANGIOTENSIN-CONVERTING ENZYME

A number of lines of evidence indicate that ACE is present in a variety of tissues, and that angiotensin II may be produced independently of the circulation. Rosenthal et al[7] isolated ACE from extracts of vascular tissues and aortic smooth muscle cells cultured in vitro.

They noted that the isoelectric point of aortic ACE was significantly different from that of ACE isolated from plasma. Strittmatter et al[8] purified an isoenzyme of ACE from rat brain. They also provided evidence that brain ACE differed from lung ACE in molecular weight and in substrate specificity. Jackson et al[9] bound an iodinated ACE inhibitor, [^{125}I]351-A, to demonstrate the existence of ACE in the testis, lung, aorta, brain and kidney.

Although ACE has been localized in the synaptosomal fraction of brain tissue,[10] relatively little is known about the subcellular location of ACE in other organs. In a recent model describing the cellular production of angiotensin II, Dzau[2] (Figure 1) proposed that angiotensin I may be converted to angiotensin II either inside or outside the cell. Kifor et al[11] and Pandey and Inagami[12] suggested that the primary site of angiotensin II production (and thus the location of ACE) is intracellular. However, Clemens et al[13] reported that ACE in mouse neuroblastoma cells was localized in plasma membranes with the active site facing outward. This is consistent with the conversion of angiotensin I to angiotensin II outside the cell in that system.

THE IMPORTANCE OF TISSUE ANGIOTENSIN-CONVERTING ENZYME IN THE CONTROL OF BLOOD PRESSURE

Traditionally, it was thought that ACE inhibitors reduced blood pressure by inhibiting ACE that circulated in plasma. The discovery that all of the components required for the production of angiotensin II exist within organs and tissues (see Dzau[2] for a review) and the fact that angiotensin II levels are higher in venous than arterial blood suggested a role for local renin–angiotensin systems in the control of blood pressure.

The importance of local production of angiotensin II was indicated by studies demonstrating that the hemodynamic effects of ACE inhibition did not have a strong temporal correlation with inhibition of this enzyme in plasma. Unger et al[14] administered 2 different ACE inhibitors, Hoe498 and MK421 (enalapril), to spontaneously hypertensive rats for 2–4 weeks. They observed that the antihypertensive potency of the drugs did not correlate with reductions in the pressor responses to intravenous administration of angiotensin I, with potentiation of bradykinin depressor responses or with decreases in plasma angiotensin II levels and urinary aldosterone excretion. They also found that treatment with enalapril at a dose of 1 mg/kg/day produced a significant decrease in blood pressure after 3 days of treatment but had no significant effect on plasma levels of ACE. They concluded that the antihypertensive actions of these ACE inhibitors were not related to their actions on the plasma renin–angiotensin system, but rather to their inhibition of ACE in tissues. They also suggested that the difference between the potencies of the 2 inhibitors may have been due to differences in the chemical characteristics of the 2 compounds, such as polarity and lipophilicity.

In another study, Unger et al[15] administered Hoe498 or enalapril to spontaneously hypertensive rats and measured plasma ACE activity and blood pressure during and after treatment (Figure 2). Both agents produced marked reductions in blood pressure and plasma ACE activity. Five days after the end of drug administration, plasma ACE activity rebounded to supranormal levels, but blood pressure remained significantly lower than normal. They concluded that plasma and tissue "pools" of converting enzyme recovered from ACE inhibitor treatment at different rates, possibly due to the accumulation of the drugs in tissue compartments. They also proposed that inhibition of ACE in peripheral tissues such as the vascular wall may be as important as the inhibition of plasma converting enzyme in explaining the antihypertensive effects of long-term ACE inhibitor administration.

Cohen and Kurz[16] evaluated inhibition of plasma and tissue ACE and mean arterial pressure after oral administration of captopril to spontaneously hypertensive rats. At 24 hours after drug administration, plasma ACE activity had returned to pretreatment values, but mean arterial pressure was still significantly reduced. At the same time, converting enzyme activity was still significantly depressed in kidney, lung, and aorta, but not in brain or heart. They concluded that inhibition of ACE in

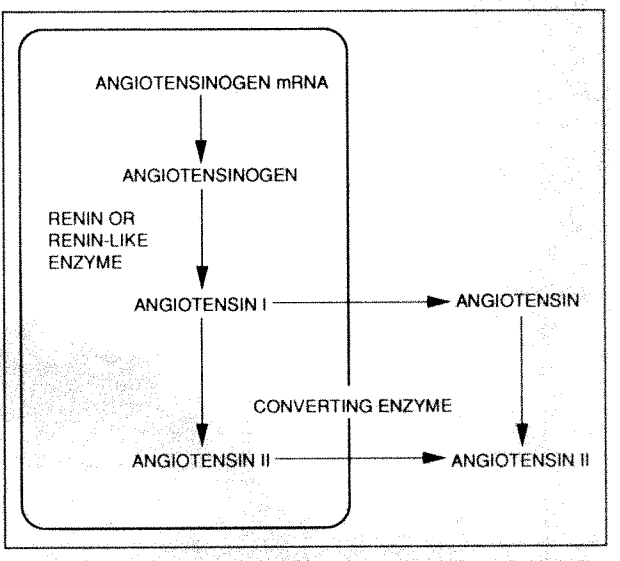


FIGURE 1. A proposed model of the intracellular renin–angiotensin system. Angiotensinogen is synthesized intracellularly and hydrolyzed by renin or a renin-like enzyme to angiotensin I. Angiotensin I is converted to angiotensin II intracellulary and then secreted. Alternatively, angiotensin I is released by the cell and converted by cell-surface converting enzyme to angiotensin II. (Reproduced with permission from *Am J Cardiol.*[2])

certain tissues may have a stronger correlation with the antihypertensive effects of ACE inhibitors than inhibition of serum enzyme activity.

Kaplan et al[17] provided further data suggesting that inhibition of plasma converting enzyme may not be the only or even the most important mechanism by which ACE inhibitors achieve their hemodynamic effects. They compared the ability of different doses of quinapril to inhibit plasma, aortic, and brain ACE in rats. They showed (Figure 3) that quinapril doses (0.03 mg/kg) that reduced plasma ACE activity by nearly 80% had almost no effect on either brain or aortic ACE activity and had only threshold antihypertensive effects. Conversely, 1.0 mg/kg doses of quinapril produced nearly 100% inhibition of plasma ACE, almost 90% inhibition of aortic ACE, and substantial reductions in blood pressure. They concluded that there was a strong correlation between the effects of quinapril on aortic ACE activity and blood pressure, but little relation between the ability of quinapril to inhibit plasma ACE and the drug's antihypertensive actions.

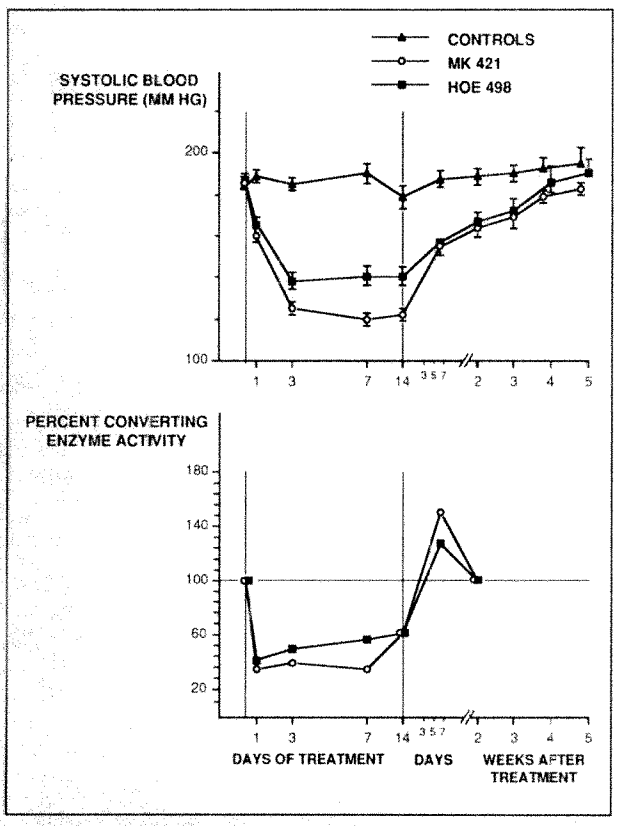


FIGURE 2. Systolic blood pressure and plasma converting enzyme activity during and after oral treatment with Hoe 498 (1 mg/kg daily) and enalapril (30 mg/kg daily) in spontaneously hypertensive rats. Enzyme activity was inhibited ($p < 0.001$) during treatment and increased ($p < 0.001$) 5 days after drug discontinuation. Blood pressure was significantly lowered ($p < 0.05$) in both groups for 2 weeks after the end of treatment. (Reproduced with permission from *J Cardiovasc Pharmacol*.[15])

Sakaguchi et al[18] used both autoradiographic and fluorimetric methods to compare the effects of single oral doses of lisinopril in rats. At 4 hours after drug administration, ACE activity was significantly reduced in serum, kidney, adrenal gland, duodenum, lung, and in the subfornical organ and the organum vasculosum of the lamina terminalis. At 24 hours after lisinopril administration, ACE in plasma had recovered to normal levels, but was still significantly below normal in all of the aforementioned tissues.

Richer et al[19] compared the pharmacokinetic and hemodynamic effects of orally administered captopril and observed that its antihypertensive action lasted well beyond the time at which the drug was demonstrated in plasma and also beyond the time at which it had any significant effect on the activity of plasma ACE (Figure 4). They suggested that the discrepancy between the pharmacokinetic profile of captopril and its clinical effects may have been due to the formation of active metabolites (e.g., captopril disulfide) whose levels were not measured in their assay. Nevertheless, it is also possible that accumulation of captopril in tissue and its inhibition of local angiotensin II production may have been the source of the difference between the hemodynamic and pharmacokinetic data obtained by them.

It has also been shown that plasma levels of ACE inhibitors do not strongly correlate with the degree of blood pressure reduction achieved by these drugs. Shaw et at[20] measured plasma free captopril concentrations and the hemodynamic response to this ACE inhibitor in patients with chronic severe heart failure. They found that plasma free captopril concentrations varied >20-fold in their patient sample, but captopril concentrations did not correlate with maximal reductions in systemic vascular resistance. Fruncillo et al[21] also reported that there was no apparent correlation between serum enalaprilat concentrations and the magnitude of blood pres-

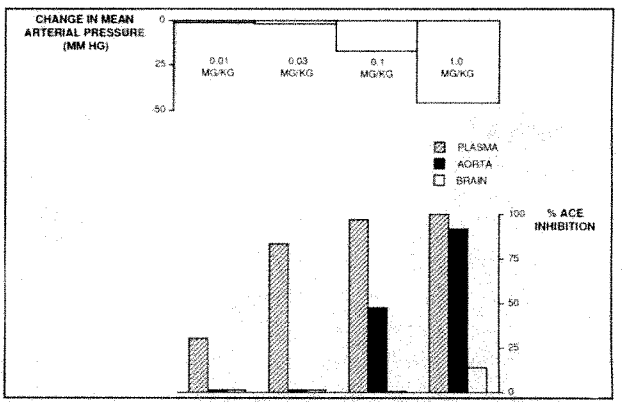


FIGURE 3. Relation between mean arterial blood pressure reduction and angiotensin-converting enzyme (ACE) inhibition with quinapril in 4 renal hypertensive (2-kidney, 1-clip Goldblatt) rats. (Reproduced with permission from *Angiology*.[17])

sure reductions. Frank et al[22] observed no significant correlation between plasma concentrations of quinaprilat, the active metabolite of quinapril, and the magnitude of blood pressure reductions in elderly hypertensive patients.

In contrast, Johnston et al[23] found that plasma enalaprilat levels were strongly correlated with the degree of inhibition of plasma ACE and reductions in blood pressure after administration of enalapril. These findings are at odds with those of Unger et al,[15] who observed that plasma ACE increased to supranormal levels whereas blood pressure remained below normal after withdrawal of enalapril from spontaneously hypertensive rats. They differ also from the results of Ohnishi et al[24] who administered enalapril orally to healthy volunteers: T_{max} occurred at 1 hour after dosing, although significant effects on blood pressure were not observed until 4 hours after drug administration.

In summary, a number of studies support the conclusion that plasma concentrations of orally administered ACE inhibitors and the resulting inhibition of plasma converting enzyme do not necessarily correlate with the antihypertensive actions of these agents. Furthermore, a strong dose–response relation between the effects of quinapril on aortic ACE activity and its effects on blood pressure has been shown.[17]

CHARACTERISTICS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Johnston et al[25] have listed a number of factors that are likely to contribute to the clinical efficacy of different ACE inhibitors (Table I). These include their oral bioavailability, the affinity with which they bind to ACE, and their tissue distribution and penetration. The bioavailability of ACE inhibitors in different tissues is influenced by a number of factors (Table II). These include lipid solubility, tissue penetration, the ability to access active transport systems, and the ability to penetrate the blood–brain barrier.

The affinity of different ACE inhibitors for converting enzyme in plasma and tissues was assessed by Johnston et al[25] by displacement of the lisinopril derivative [^{125}I]351-A. In plasma, lung, kidney (Figure 5), and the 4 chambers of the heart (Figure 6), the IC_{50} values of quinaprilat were lower than those of benazeprilat, perindoprilat, lisinopril, or fosinoprilat. Fabris et al[26] also compared the ability of quinaprilat, benazeprilat, perindoprilat, fosinoprilat and

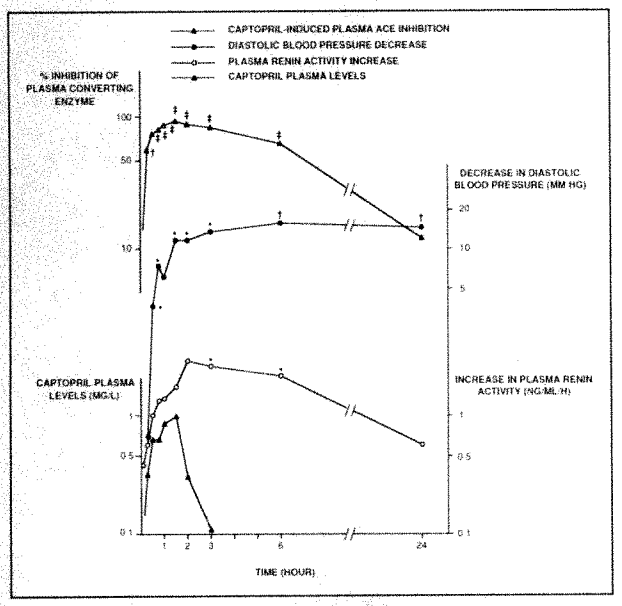


FIGURE 4. Kinetics of captopril plasma levels, captopril-induced plasma angiotensin-converting enzyme (ACE) inhibition, plasma renin activity increase, and diastolic blood pressure decrease. *p <0.05; †p <0.01; ‡p <0.001 (compared with pretreatment values). (Reproduced with permission from *Br J Clin Pharmacol*.[19])

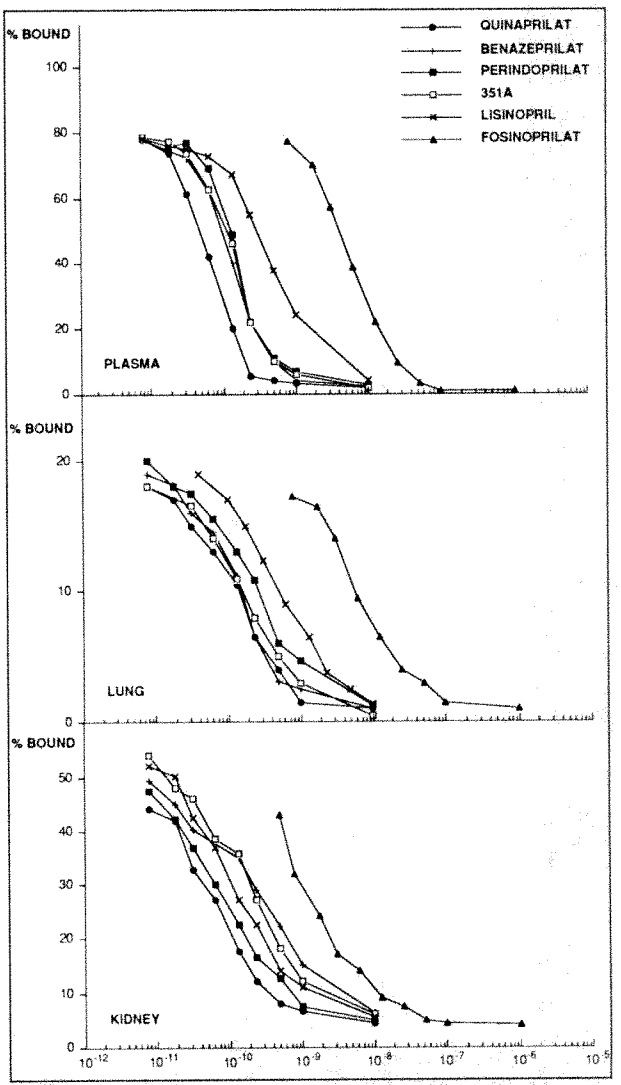


FIGURE 5. Displacement curves of [^{125}I]351-A (percentage bound) in tissue homogenates from rat lung and kidney compared with rat plasma ACE for 6 angiotensin-converting enzyme inhibitors: quinaprilat; benazeprilat; perindoprilat; 351A; lisinopril; and fosinoprilat. (Reproduced with permission from *J Hypertens*.[25])

TABLE I Features that Differentiate ACE Inhibitors

Pharmacokinetics
Chemical structures (SH group)
Prodrugs (ester/diacid)
Oral and tissue bioavailability
Lipid solubility (ester/diacid)
Binding affinity
Metabolism
Active metabolites
Hepatic route
Renal excretion
Pharmacodynamics
Potency
Binding affinity and characteristics
Tissue bioavailability
Regional blood flow
Non-angiotensin effects
Bradykinin
Prostaglandins
Free radical scavenger

Reproduced with permission from J Hypertens.[25]
ACE = angiotensin-converting enzyme; SH = spontaneously hypertensive.

TABLE II Factors that Influence the Tissue Bioavailability of ACE Inhibitors

Plasma concentration
Lipid solubility (prodrug/diacid)
Tissue penetration (ester/diacid)
Active transport system
Blood-tissue barrier (brain, testis)
Tissue esterase activity

Reproduced with permission from J Hypertens.[25]
Abbreviation as in Table I.

lisinopril to displace [^{125}I]351-A from membrane homogenates of the rat heart. Their results indicated the following "order of potency": quinaprilat = benazeprilat >perindoprilat >lisinopril >fosinoprilat. Together these data indicate that quinaprilat has a high affinity for cardiac converting enzyme. Fabris et al[26] suggested that the order of potency of the tested inhibitors may relate to differences in the lipophilicity of these agents. It is not clear, however, whether this is due to differential penetration of the membrane environment by inhibitors, or specifically due to differences in inhibitor affinity for enzyme. Whereas the lipophilicities of ACE inhibitors have not been estimated, Johnston et al[25] noted that esterified prodrugs such as quinapril are more lipid soluble than active diacids such as quinaprilat, and that the former may more readily penetrate tissues. Therefore, the chemical nature of ACE inhibitors may be significant not only in determining the binding of the inhibitor to ACE, but also in determining the concentration of inhibitor in the lipophilic membranous environment of the enzyme.

In this regard we may note that esterified prodrugs such as quinapril have considerable ACE inhibitory activity and their relative abilities to penetrate tissues may be an important determinant in differences in activity. Thus, Kaplan et al[27] evaluated the ability of quinapril,

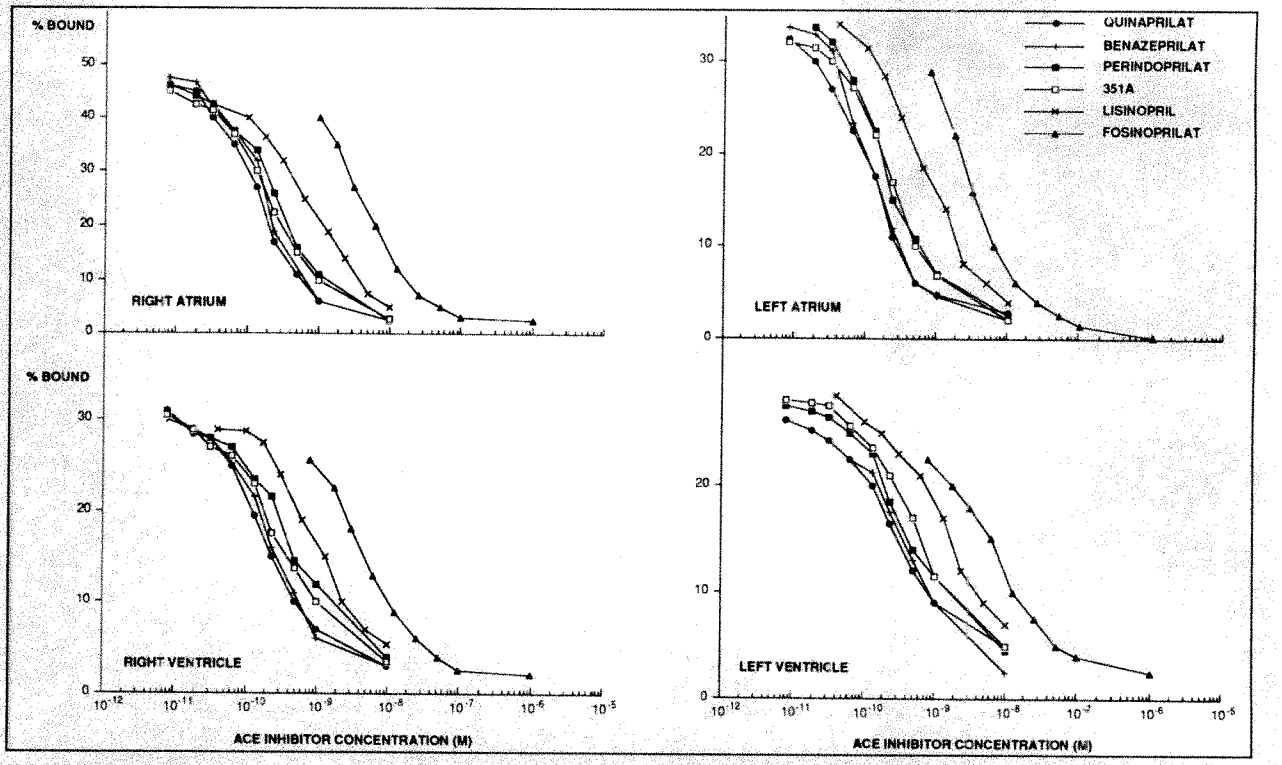


FIGURE 6. Displacement curves of [^{125}I]351-A from the 4 chambers of the heart by 6 angiotensin-converting enzyme (ACE) inhibitors: quinaprilat; benazeprilat; perindoprilat; 351A; lisinopril; and fosinoprilat. (Reproduced with permission from *J Hypertens.*[25])

enalapril, and captopril to inhibit ACE from guinea pig serum (Figure 7) and found that the molar concentration of quinapril required to achieve 100% inhibition of ACE was <10% of that required to achieve the same inhibition level with either enalapril or captopril.

Some ACE inhibitors are capable of penetrating the blood–brain barrier if they are administered in high doses. Jackson et al[9] have shown that oral gavage with perindopril 16–32 mg/kg reduced brain ACE activity. Johnston et al[25] also demonstrated that increasing doses of perindopril progressively inhibited ACE activity in rat caudate putamen and globus pallidus. Cohen and Kurz[16] provided similar data for enalapril, showing a dose-proportional inhibition of brain enzyme in rats.

On the other hand, Kaplan et al[27] demonstrated that oral administration of either 0.1 or 1.0 mg/kg of quinapril to rats failed to inhibit brain ACE, although plasma and aortic ACE were inhibited. The lack of effect of quinapril on brain ACE activity was confirmed by Johnston et al.[25] After administration of [^{14}C]quinapril, the radiolabeled quinapril distributed rapidly and extensively to all tissues except the brain in rats.[28] Heald and Ita[29] also reported that radiolabeled captopril did not penetrate the central nervous system in rats.

CLINICAL SIGNIFICANCE OF DIFFERENCES IN THE PROPERTIES OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE inhibitors differ in their ability to penetrate different tissues and to bind to tissue ACE. These properties may relate to the relative polarity or lipophilicity of the inhibitor. It would be surprising if such differences were not reflected in differences in clinical efficacy. For example, both quinapril and quinaprilat have lower IC_{50} values for ACE inhibition than captopril.[27] Furthermore, administration of 1.0 mg/kg of quinapril to hypertensive rats resulted in near-complete inhibition of both plasma and aortic ACE activity, but reduced brain ACE activity by <15%.[27] Cohen and Kurz[16] showed that 10 mg/kg captopril was required to achieve similar inhibition of aortic and plasma ACE in spontaneously hypertensive rats, but captopril also produced a 73.7% reduction in brain ACE activity. The significance of this difference between captopril and quinapril in penetrating the central nervous system remains to be fully elucidated, but it seems to have little bearing on the control of hypertension. For example, in a multicenter double-blind study of 172 patients with moderate to severe hypertension, twice-daily administration of quinapril with a total dose of 20–80 mg/day was significantly more effective than captopril (50–200 mg/day).[30] After a minimum of 4 weeks of treatment, evaluable patients showed a significantly greater reduction in diastolic blood pressure in the quinapril group than in the captopril group (18.6 vs 15.3 mm Hg, respectively, $p < 0.05$).

CONCLUSION

The studies summarized in this review strongly support the concept that tissue renin–angiotensin systems are likely to play a very important role in the control of blood pressure. The data also support the conclusion that different ACE inhibitors vary significantly in their abilities to penetrate tissue and bind to converting enzyme. Several investigators have suggested that these differences may be closely related to the relative lipophilicity of these agents. Finally, correlation of experimental and clinical data provided preliminary indications that differences in the properties of ACE inhibitors that have been established by in vitro and animal experimentation may

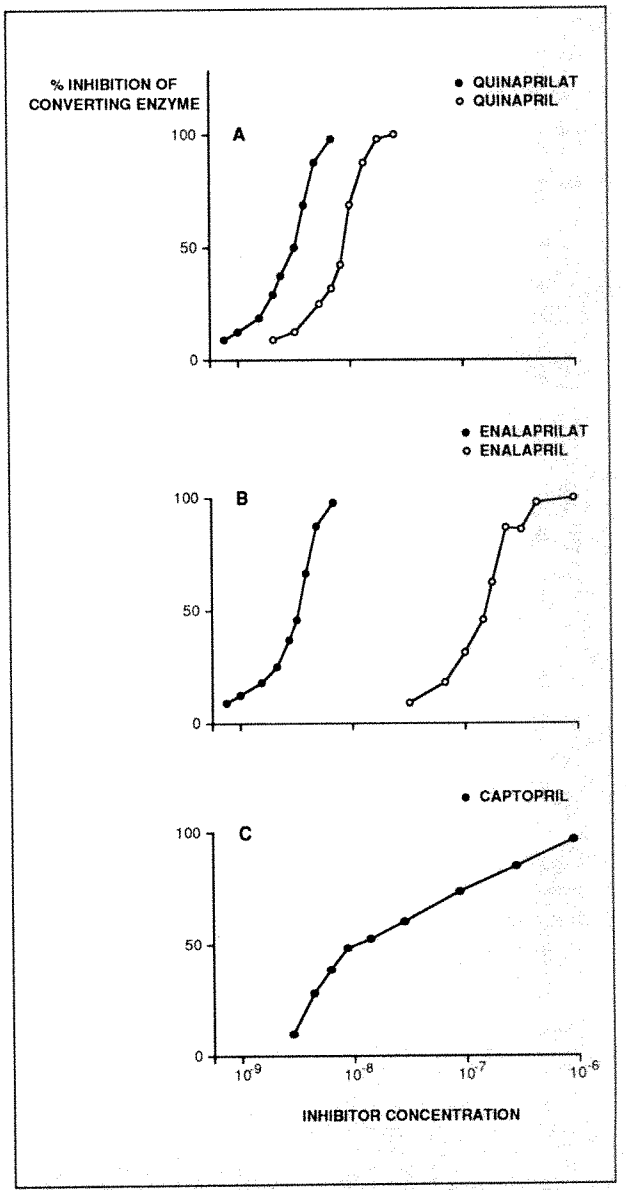


FIGURE 7. Inhibition of angiotensin-converting enzyme from guinea pig serum by: *A*, quinapril and quinaprilat; *B*, enalapril and enalaprilat; and *C*, captopril. (Adapted from Kaplan et al.[27])

have considerable predictive value with respect to the clinical efficacy of these drugs.

Further advances in the treatment of hypertension with ACE inhibitors are likely to arise from continuing evaluation of the effects of existing and newly developed drugs in isolated tissue, as well as an advancement in our understanding of the role that local renin–angiotensin systems play in the control of blood pressure.

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Effects of Antihypertensive Agents on Coronary Artery Disease Risk Factors

James A. Schoenberger, MD

The adverse effects of certain antihypertensive medications, most notably diuretics and β blockers, on serum lipids, glucose, and potassium may explain why control of hypertension has not been accompanied by declines in coronary artery disease. Evidence indicates that angiotensin-converting enzyme (ACE) inhibitors, including quinapril, the newest member of this class of drugs, have no deleterious effects on these coronary risk factors. In addition to differences in chemical structure, the unique activity of quinapril at the local tissue level might to some degree explain its comparatively favorable clinical profile. Consequently, ACE inhibiting agents may be better choices for the management of patients with mild-to-moderately elevated blood pressure. However, controlled clinical trials with these drugs are needed to determine their impact on events related to coronary artery disease.

(Am J Cardiol 1992;69:33C–39C)

In the Framingham Study, both diastolic and systolic blood pressure levels were correlated to risk of coronary artery disease (Figure 1).[1] Study participants with systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg were at a two- to threefold higher risk of coronary artery disease than those with lower blood pressure levels. Borderline hypertension, defined as a systolic blood pressure of 140–159 mm Hg and a diastolic blood pressure of 90–94 mm Hg, was associated with a 50% increase in the rate of coronary artery disease in the study cohort.

Pooling Project data obtained from more than 7,000 middle-aged white men also demonstrated a relation between blood pressure and the risk of a major coronary event.[2] Mean systolic blood pressure was significantly higher in men who experienced a first coronary event during the follow-up periods of the various individual studies included in the project. This was true for all 4 age groups examined: 40–44, 45–49, 50–54, and 55–59 years. The magnitude of the difference ranged from 5 to 7 mm Hg in the 3 younger groups. Mean systolic blood pressure in 55- to 59-year-old men who experienced coronary events was 13 mm Hg higher than in those in whom such events did not occur.

Combined data from 5 of the epidemiologic studies included in the Pooling Project showed that the age-adjusted risk of a new coronary event in men with systolic blood pressure ≤120 mm Hg was only 70% of the average risk. In contrast, the risk in those with systolic blood pressure >150 mm Hg was 50% greater than average.

The risk of a first major coronary event was likewise associated with the level of diastolic blood pressure. Mean diastolic blood pressures were 3.5–6.5 mm Hg higher in study subjects who experienced such an event. The age-adjusted risk increased from only 72% of the average risk in men with diastolic blood pressure ≤76 mm Hg to 156% of the average risk in those with a diastolic blood pressure >93 mm Hg.

IMPACT OF ANTIHYPERTENSIVE THERAPY ON CORONARY ARTERY DISEASE

Results of these epidemiologic investigations suggested that control of hypertension might reduce the risk of coronary artery disease. Such a beneficial effect has indeed been noted in patients with severe blood pressure elevations. Men with a diastolic blood pressure of 115–129 mm Hg at the time of admission to the Veterans Administration Cooperative Trial responded to antihy-

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pertensive therapy with a 93% reduction in the annual incidence of serious morbid or fatal cardiovascular events.[3] The value of antihypertensive therapy in preventing events related to coronary artery disease in patients with less severely elevated blood pressure is not as clear.

Most of the prospective trials conducted to evaluate the effect of a pharmacologic reduction of mild to moderately elevated blood pressure on mortality and morbidity have demonstrated a decline in hypertension-related events, such as stroke, congestive heart failure, progression to severe hypertension, and renal failure.[4–6] In contrast, coronary artery disease has generally remained unaffected. In the Oslo Study, the actively treated group actually experienced a higher incidence of fatal and nonfatal coronary events than the control group.[4,5] In the Multiple Risk Factor Intervention Trial (MRFIT), an excess of sudden deaths was noted among those patients with nonspecific electrocardiographic abnormalities at the time of entry into the study who were assigned to vigorous coronary risk factor reduction therapy at special clinics.[3]

Adverse effects on coronary risk factors mediated by the drugs used to lower blood pressure have been proposed as a possible explanation for the very modest, if any, beneficial effects of antihypertensive therapy on the incidence of coronary events.[6,7] This theory is supported by the fact that the treatment regimens used in virtually all of these trials included diuretics, β-adrenergic blockers, or both, agents known to have an adverse impact on certain coronary artery disease risk factors, including serum lipid, glucose, and potassium levels.

A number of widely used antihypertensive agents are known to affect serum lipids adversely. A review by Weidmann et al[8] indicates that thiazide diuretics cause a slight increase in total cholesterol and significant increases in low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol.

Ames[4,7] used coronary risk tables developed from Framingham data to determine the impact of diuretic-induced changes in serum lipids on the probability of developing coronary artery disease. His analysis showed that the 15 mg/dL increase in total cholesterol associated with chlorthalidone therapy offset the decline in coronary artery disease expected as a result of a drug-induced reduction in blood pressure by 25%. The small 12 mg/dL increase in total cholesterol that occurred in patients treated with hydrochlorothiazide offset the beneficial blood pressure-lowering effects of this drug by 50%.

For the past several years, β-adrenergic blocking agents have been regarded as an alternative to diuretics for the initial management of hypertension. A review of reports of the influence of β blockers on serum lipids shows that these drugs generally increase total and VLDL triglycerides by approximately 25 and 40%, respectively, and decrease high-density lipoprotein cholesterol by approximately 10% (Figure 2).[8] Total cholesterol and LDL cholesterol are largely unaffected by β-blocker therapy.

It appears that cardioselective agents such as atenolol or metoprolol may have a lesser effect on triglyceride levels than nonselective β blockers such as propranolol and oxprenolol.[6] However, significant increases in VLDL and significant decreases in HDL cholesterol have been noted with both selective and nonselective drugs. There is also evidence that β blockers with intrinsic sympathomimetic activity such as pindolol may not significantly affect total cholesterol, HDL cholesterol, or triglyceride levels.

The impact of other forms of antihypertensive therapy on serum lipids is less clear. Evaluation of the effects of sympatholytic agents, such as methyldopa, clonidine, and

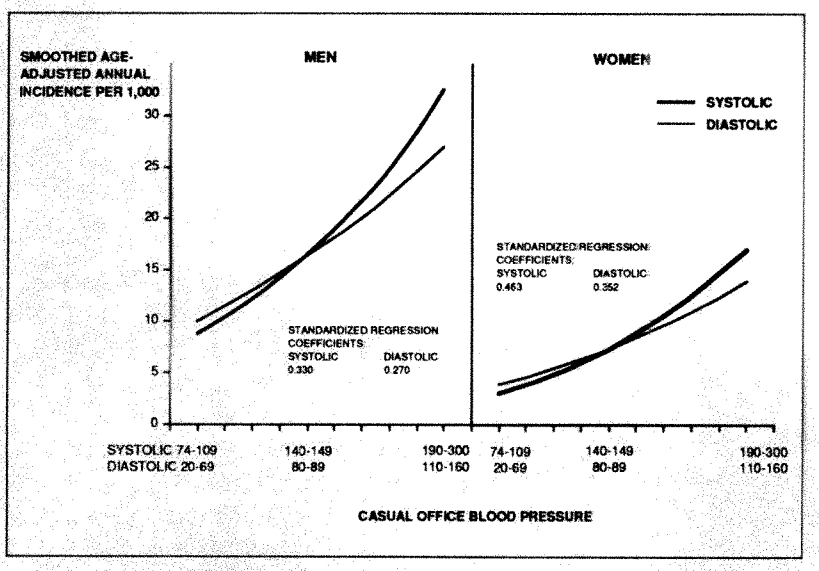


FIGURE 1. Incidence of coronary artery disease over a 20-year follow-up period according to systolic and diastolic blood pressure levels in male and female Framingham study participants between the ages of 45 and 74 years. (From Castelli.[1])

guanabenz, is complicated by the fact that these drugs are seldom used as monotherapy but rather in combination with a diuretic or a β blocker. The limited data that are available suggest that clonidine may reduce total plasma cholesterol.[6] Changes reported with methyldopa include reductions in total, HDL, and LDL cholesterol and both increases and decreases in total triglyceride levels.[6,8]

Direct vasodilators, which include hydralazine and minoxidil, do not appear to have a significant effect on serum lipids. When given alone, however, these agents cause reflex stimulation of the sympathetic nervous system and the renin–angiotensin system, resulting in increases in heart rate and myocardial oxygen consumption and retention of salt and water.[6] To blunt this compensatory activity, these drugs must frequently be given along with β blockers and diuretics, which, as previously discussed, have potentially detrimental effects on serum lipid profiles.

Although they do produce a number of central nervous system or cardiovascular side effects, or both, calcium antagonists and post-synaptic α-receptor blockers, such as prazosin, appear to have little or no significant effects on lipid metabolism or serum lipid and lipoprotein levels.[8]

DIABETES MELLITUS AND IMPAIRED GLUCOSE TOLERANCE

The increased susceptibility of diabetic patients to coronary artery disease is well recognized. It has been suggested that patients with drug-induced impairment of carbohydrate metabolism may also be at an increased risk for the same coronary complications associated with overt diabetes mellitus.[9]

This theory is supported by 16-year follow-up data from the Framingham Study, which showed a relation between blood glucose levels and coronary artery disease. A modest increase in coronary risk was noted even in those Framingham participants with blood glucose levels within the usually accepted range (Figure 3).[1] A much more dramatic increase in risk was apparent at the high glucose levels characteristic of diabetes mellitus.

Similar to serum lipids, serum glucose levels may also be adversely affected by antihypertensive therapy. Alterations in glucose metabolism ranging from asymptomat-

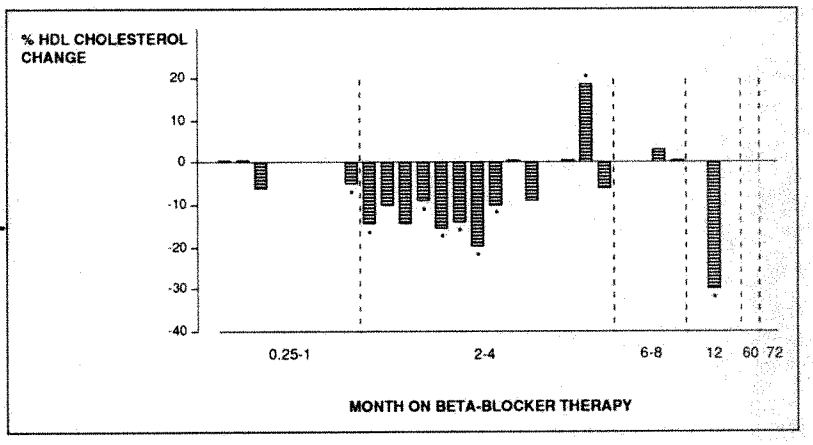


FIGURE 2. Percentage changes in high-density lipoprotein (HDL) cholesterol with β-blocker therapy based on an analysis of published reports. *Asterisks* denote statistically significant changes compared with placebo administration ($p \leq 0.05$). (From Weidmann et al.[5])

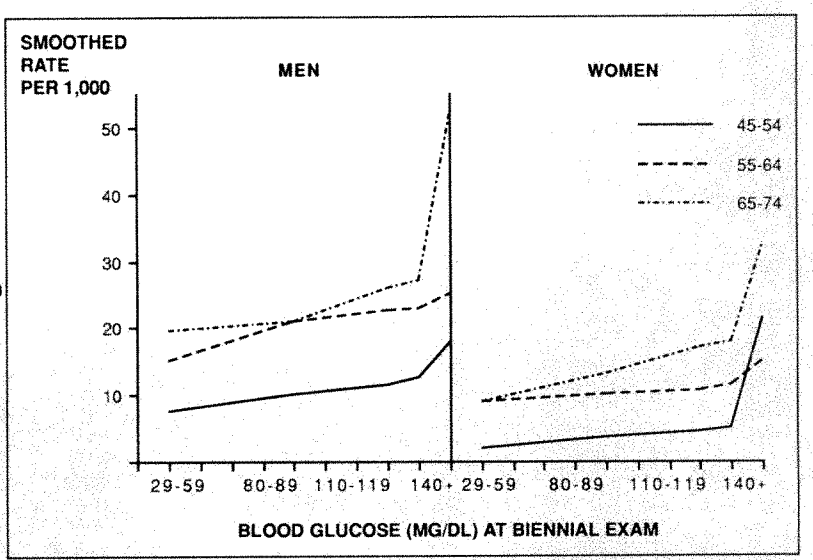


FIGURE 3. Average annual incidence of coronary artery disease over a 16-year follow-up period according to blood glucose level in male and female Framingham Study participants 45–74 years of age. (From Castelli.[1])

ic impairment of glucose tolerance to overt diabetes mellitus have been reported in patients treated with thiazide diuretics.[10] Data reviewed by Sowers[11] show a progressive deterioration of glucose tolerance in hypertensive patients over a 14-year period of continuous therapy with thiazide diuretics. Discontinuation of these drugs resulted in an improvement in glucose tolerance (Figure 4). Hypertensive patients treated with diuretic-based regimens by Ames[4] also demonstrated significantly higher glucose levels during therapy than after withdrawal of these drugs. In contrast to the ACE inhibitor captopril, Pollare et al[12] reported significant decreases in the insulin-mediated disposal of glucose in patients treated with hydrochlorothiazide ($p < 0.01$), as well as increases in basal insulin secretion and the late insulin response to glucose. A reduction in serum potassium levels induced by diuretic therapy has been proposed as a contributing factor, if not the primary mechanism, for diuretic-induced changes in glucose metabolism.[9] The prevention of diuretic-induced hyperglycemia by the use of potassium supplementation supports this explanation.[13]

Impaired glucose tolerance may also be a concern with the use of clonidine, prazosin, calcium antagonists, and β-adrenergic blockers. A longitudinal population study conducted in Sweden demonstrated an increased risk of diabetes in hypertensive women treated with β blockers, diuretics, or a combination of these 2 types of drugs.[14] Mohler et al[15] reported the development of overt diabetes mellitus in 7 of 40 hypertensive patients treated with the β blocker propranolol for >6 months. An additional 16 patients exhibited abnormalities in glucose tolerance. Inhibition of insulin secretion, which may be unrelated to blockade of β-adrenergic receptors,[9] appears to be the mechanism responsible for the alterations in glucose metabolism observed with β-blocker therapy.

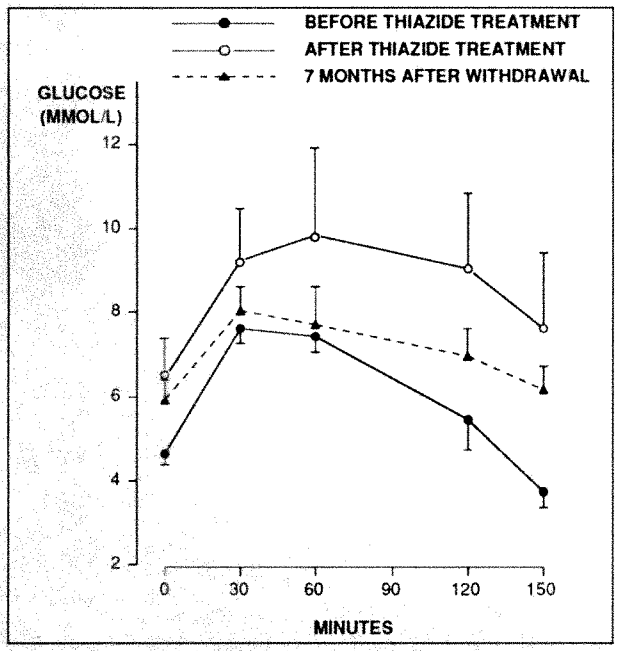


FIGURE 4. Results of oral glucose tolerance tests in 10 hypertensive patients before and after 14 years of thiazide treatment and 7 months after thiazide withdrawal. (From Sowers.[11])

HYPOKALEMIA

Hypokalemia is a common, well-recognized complication of diuretic administration. MRFIT findings generated a renewed interest in the clinical significance of this metabolic alteration. Patients in this trial with baseline resting electrocardiographic abnormalities who received risk factor reduction therapy (including blood pressure-lowering medication) at special clinics demonstrated a 61% higher rate of death attributable to coronary artery disease than similar patients referred to their usual source of care within the community.[3] Diuretic-induced hypokalemia was suggested as a possible cause of the increased death rate in the special intervention group.

The daily doses of 100 mg of hydrochlorothiazide or chlorthalidone used in treating many of the hypertensive patients in the MRFIT cohort were larger than those received by most hypertensive study subjects assigned to usual care.[3] Furthermore, the serum potassium levels of 3.38 mEq/liter reported with this dose level is lower than the threshold level of 3.5 mEq/liter below which there is a sharp increase in the incidence of ventricular arrhythmias.

The association between hypokalemia and ventricular ectopic activity has been recognized for a number of years. The first prospective investigation of the frequency of ventricular ectopy in nondigitalized patients with diuretic-induced hypokalemia was conducted by Holland et al[16] in 1981. Their study involved 21 patients with mild hypertension in whom plasma potassium had declined to <3.5 mEq/liter during previous diuretic therapy. Overall, 7 patients developed ventricular ectopic activity after 4 weeks of treatment with 50 mg of hydrochlorothiazide twice daily. Four of these patients showed evidence of complex ventricular activity, consisting of multifocal ventricular premature beats, ventricular couplets, ventricular tachycardia, or a combination of these. Ectopy was attenuated when spironolactone was added to or substituted for hydrochlorothiazide.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme (ACE) inhibitors, which are used in the management of both hypertension and congestive heart failure, act by blocking the activity of ACE, the enzyme responsible for the conversion of the inactive decapeptide angiotensin I to the potent vasoconstrictor angiotensin II. In contrast to other classes of antihypertensive agents, these drugs have demonstrated no significant adverse effects on coronary risk factors.[17]

The prototype ACE inhibitor, captopril, first became available for clinical use in 1981. During the early years after the introduction of this drug, a high incidence of rash, taste disturbances, proteinuria, and neutropenia was reported in captopril-treated patients.[17,18] The incidence of such side effects was subsequently found to be related to a number of factors, including the sulfhydryl group present in the captopril molecule, the high doses of the drug that were used initially, and the health status of the population originally treated with this drug (i.e., primarily patients with severe, complicated hypertension often accompanied by renal impairment and collagen vascular disease).[18] Subsequent research resulted in the development of ACE inhibitors devoid of the sulfhydryl group. These newer agents, which include lisinopril, enalapril, and quinapril, appear to have a favorable safety profile compared with captopril at high doses.[17,19,20]

Neither captopril nor the newer ACE inhibiting agents have been found to significantly affect serum cholesterol levels, glucose metabolism, or potassium balance.[17] In fact, a slight increase in serum potassium, believed to be related to the effect of these drugs on aldosterone, has been observed with the use of ACE inhibitors as monotherapy.[17,20] When given in combination with a diuretic, these agents may attenuate the decline in serum potassium generally associated with diuretics.[17]

QUINAPRIL, A NEW ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

Quinapril is a new nonsulfhydryl ACE inhibitor that is generally better tolerated than captopril or enalapril.[21] The effectiveness of quinapril in the management of mild to moderate hypertension has been established.[22,23]

Quinapril has been shown to be significantly more effective than captopril in the treatment of moderate to severe hypertension.[24] The mean decrease of 18.2 mm Hg in diastolic blood pressure with quinapril in this study was significantly ($p < 0.05$) greater than the 14.8 mm Hg mean decrease in diastolic blood pressure observed with captopril, based on an intent-to-treat analysis of all patients with a blood pressure measurement within the specified time window (8–16 hours after the dose). The percentage of patients who had adequate control of diastolic blood pressure at the low or middle ACE inhibitor dosages was twice as high for quinapril as for captopril.

After oral ingestion, quinapril is hydrolyzed to its diacid, quinaprilat, a more active ACE-inhibiting compound than the parent drug. In vitro studies have shown that quinaprilat markedly inhibits plasma ACE activity.[25] Orally administered quinapril attenuates the pressor response to angiotensin I in both animals and humans.[25,26] The hypotensive response of renal hypertensive rats to quinapril has been found to correlate better with aortic ACE inhibition than with plasma inhibition of the enzyme.[25] This observation is in agreement with other experimental data that suggest that inhibition of ACE at the local tissue level may be more important to the blood pressure-lowering effect of ACE inhibitors than plasma ACE inhibition.[27] Specifically, vascular tissue ACE inhibition may be more predictive of the antihypertensive activity and overall clinical profile of quinapril than plasma ACE inhibition.

Extensive safety evaluations in >2,000 patients with hypertension and congestive heart failure who received quinapril during long-term, double-blind, and open-label trials indicate that this new ACE inhibitor is very well tolerated.[21] Adverse events in quinapril-treated patients have generally been mild and transient and have seldom necessitated discontinuation of the drug. Furthermore, no significant adverse effects on serum lipid, glucose, or potassium levels have been detected with quinapril.

TABLE I Effect of Quinapril on Plasma Lipids in Rats

Diet/Model	Route	Dose (mg/kg)	Cholesterol (% Change)	Triglyceride (% Change)
Cholesterol-fed	Oral	50	−12, −34*	−39, −41
Cholesterol-fed	Oral	1	−9 (NS)	−15 (NS)
		3	−3 (NS)	−18 (NS)
		10	−8 (NS)	−10 (NS)
Chow-fed	Oral	3	−17	−12
		10	−25	−34
Fructose-fed	Intraperitoneal	3	—	+4 (NS)
		10	—	+4 (NS)

Reproduced with permission from Kaplan.[25]
* Results using 2 different rat strains.
N = 5 to 9 rats/group; NS = not significant.

EFFECT OF QUINAPRIL ON SERUM LIPOPROTEINS

Studies in animals: The preclinical evaluation of quinapril in animals included an investigation of the effect of this drug on serum lipids and lipoproteins. These studies were conducted in various rat models with oral or intraperitoneal quinapril, or both.[25]

Plasma cholesterol and triglyceride levels in cholesterol-fed rats were unaffected by oral administration of quinapril at doses of 1–10 mg/kg/day for 1 week. However, increasing the quinapril dosage to 50 mg/kg/day resulted in significant reductions of 34% in plasma cholesterol and 41% in plasma triglycerides (Table I).

Chow-fed rats treated orally with 10 mg/kg of quinapril showed a 34% decrease in plasma triglycerides. Cholesterol levels in these animals declined by 25%. The failure of intraperitoneal doses of 3 and 10 mg/kg of quinapril to prevent hypertriglyceridemia in fructose-fed rats suggested that the drug has no effect on lipogenesis and synthesis of VLDLs.

Studies in humans: The most reliable indication of the effect of quinapril on serum lipids is provided by the results of a Finnish study that specifically examined both

TABLE II Serum Lipids and Lipoproteins in Hypertensive Patients During Treatment with Quinapril or Placebo

	Quinapril (n = 16)	Placebo (n = 7)	p Value
Baseline			
Chol	6.1 ± 1.6	6.8 ± 1.1	NS
Tg	2.3 ± 2.0	1.7 ± 0.9	NS
HDL	1.28 ± 0.34	1.32 ± 0.57	NS
LDL	4.1 ± 1.5	4.8 ± 0.9	NS
HDL/LDL	0.34 ± 0.11	0.27 ± 0.11	NS
12 weeks			
Chol	6.1 ± 1.5	6.7 ± 1.2	NS
Tg	2.1 ± 1.3	1.5 ± 0.5	NS
HDL	1.32 ± 0.33	1.46 ± 0.52	NS
LDL	3.9 ± 1.4	4.7 ± 1.0	NS
HDL/LDL	0.36 ± 0.12	0.31 ± 0.08	NS
1 year*			
Chol	6.3 ± 1.5		
Tg	2.2 ± 2.1		
HDL	1.26 ± 0.37		
LDL	4.2 ± 1.4		
HDL/LDL	0.34 ± 0.15		
	p = NS		

Reproduced with permission from Koskinen et al.[28]
* n = 13.
Chol = total cholesterol; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; NS = not significant; Tg = triglycerides.

the short- and long-term effects of quinapril on serum triglycerides and on total, HDL, and LDL cholesterol in humans.[28]

The 23 subjects enrolled in this study included 12 postmenopausal women and 11 men with mild to moderate hypertension. After a 2- to 4-week, single-blind, placebo washout period, 16 of these patients were randomly assigned to receive quinapril at an initial dosage of 20 mg/day. The quinapril dosage level was subsequently doubled at 4-week intervals, resulting in a final dosage of 80 mg/day at the end of the initial 12-week study period. The other 7 patients were treated with placebo. After 12 weeks of treatment, both quinapril- and placebo-treated patients showed only minimal changes in serum lipid and lipoprotein concentrations and in the HDL/LDL ratio (Table II). Values for these parameters did not differ significantly between the 2 groups.

At the end of the initial 12 weeks of this study, 13 of the participants continued to receive quinapril on an open-label basis for an additional 9 months. The quinapril doses used during this phase of the study were those previously found to control blood pressure in each patient. Ten patients were treated with 40 mg of the drug daily and the other 3 received 20 mg. No significant changes in serum lipid and lipoprotein levels were apparent in these patients after a total of 1 year of combined double-blind and open-label therapy.

EFFECT OF QUINAPRIL ON SERUM GLUCOSE

Data on changes in urinary glucose concentrations are available for patients with both hypertension and congestive heart failure who participated in long-term, double-blind, and open-label studies with quinapril. Most of the patients evaluated had normal urinary levels at the end of treatment, and <2% of these study subjects demonstrated elevated levels at the end of treatment. Of 48 patients with high urinary glucose concentrations at baseline, 28 (58%) had normal levels by the end of the study.

EFFECT OF QUINAPRIL ON SERUM POTASSIUM

Safety data from patients with hypertension or congestive heart failure who were treated with quinapril during clinical trials indicate that the drug has a minimal effect on serum potassium (Table III).[29] Overall, hypokalemia was detected in only 3% of all patients who received quinapril, either with or without a diuretic. Those who received quinapril as monotherapy had a 2% incidence of hypokalemia, similar to that in the placebo (3%), captopril (2%) and enalapril (4%) treatment groups.

The incidence of hypokalemia in patients who received quinapril along with a diuretic, 7%, was higher than in those treated with quinapril monotherapy. However, this incidence was still well below the 31% rate of hypokalemia in patients treated with chlorthalidone. This observation suggests that concomitant administration of quinapril may attenuate the hypokalemic effect of diuretic therapy.

Hyperkalemia was detected in only 2% of all patients who received quinapril, with or without a diuretic, and in 3% of those treated with quinapril as monotherapy. These rates compared favorably with those observed in patients treated with placebo (2%), with captopril (1%) and with enalapril (3%).

TABLE III Incidence of Changes in Serum Potassium in Patients with Hypertension or Congestive Heart Failure During Double-Blind Clinical Trials with Quinapril

	Percentage of Patients						
	Quinapril ± Diuretic	Quinapril Monotherapy	Quinapril + Diuretic	Placebo ± Diuretic	Captopril ± Diuretic	Enalapril ± Diuretic	Chlorthalidone Monotherapy
Hypokalemia	3	2	7	3	2	4	31
Hyperkalemia	2	3	—	2	1	3	0

CONCLUSION

The available evidence indicates that ACE inhibitors have no deleterious effects on significant coronary artery disease risk factors, including serum lipids, glucose, and potassium. Consequently, these agents may be better choices than diuretics or β blockers for the management of patients with mild-to-moderately elevated blood pressure. Future controlled clinical trials will determine the effects of ACE inhibitors on the incidence of events related to coronary artery disease.

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Effects of Inhibitors of Angiotensin-Converting Enzyme on Regional Hemodynamics

John S. Banas, Jr., MD

Inhibitors of angiotensin-converting enzyme (ACE) exert favorable regional hemodynamic effects at various sites. In patients with essential hypertension, ACE inhibitors reduce renal vascular resistance while enhancing renal blood flow, glomerular filtration rate, and acute and sustained natriuresis. Whereas these agents may either reduce or have no effect on hepatic blood flow, they are associated with reduced splanchnic resistance. ACE inhibitors reduce total peripheral resistance and may maintain limb blood flow. In normal subjects, they augment blood flow to skeletal muscle and skin and reduce peripheral resistance in vessels supplying these regions. ACE inhibitors appear to exert a vasodilatory effect on large arteries as well as arterioles. Dilatation is often accompanied by significant improvements in arterial compliance, possibly due to direct effects of the renin–angiotensin system on the arterial wall. Reduction of blood pressure is generally not accompanied by reduced cerebral blood flow. Enhanced tissue effects of newer ACE inhibitors such as quinapril may result in improved regional hemodynamic effects.

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In essential hypertension, the primary hemodynamic disturbance is an increase in total systemic vascular resistance. If the condition deteriorates, the hemodynamic pattern may be associated with reduced left ventricular compliance, left ventricular hypertrophy and reduced blood flow to the brain, kidneys, and myocardium.[1] Therefore, major goals of antihypertensive therapy are to reduce elevated peripheral resistance and maintain adequate regional blood flow.

While regional hemodynamics are responsive to local metabolic needs, other factors alter local perfusion.[2] Hyperactivity of the renin–angiotensin system has been related to changes in resistance vessels, and it has been established that increased levels of angiotensin II contribute significantly to hypertension.[3] Angiotensin II, by its hemodynamic and tubular effects, modulates renal sodium and water excretion and has an important role in blood pressure regulation (Figure 1).[4]

Angiotensin-converting enzyme (ACE) inhibitors block the vasoconstricting effects of angiotensin II, thereby reducing vascular resistance. In animals and humans, blood pressure reduction with some ACE inhibitors, especially quinapril, a new nonsulfhydryl ACE inhibitor, correlates well with ACE levels and inhibition in vascular tissues (Figure 2).[5]

EFFECT OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS ON RENAL BLOOD FLOW

Because the renin–angiotensin system is closely connected to the kidney, many effects of ACE inhibitors on the functioning of both normal and diseased kidneys have been identified.[6,7] Modification of the activity of the renin–angiotensin–aldosterone system may produce favorable renal responses, including reduction of renal vascular resistance, enhancement of renal blood flow and glomerular filtration rate, acute natriuresis, sustained diuresis, and a decrease in urinary protein excretion.[8] In patients with primary essential hypertension, therapy with ACE inhibitors has reduced renal vascular resistance, sustaining or improving renal blood flow and glomerular filtration rate, as well as resetting sodium and water balance and sparing potassium loss (Table I).[8]

Despite pharmacokinetic differences, all ACE inhibitors seem to have beneficial effects on renal blood flow.[7,9] The renal hemodynamic effects of quinapril are similar to those of enalapril, and captopril. In a recent study,

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Kaplan et al[5] determined the renal hemodynamic effects of quinapril, captopril, enalapril, or saline in sodium pentobarbital-anesthetized dogs. Similar to older ACE inhibitors, quinapril produced a dose-dependent elevation in renal blood flow and a reduction in renal vascular resistance (Figures 3 and 4).

The renovascular effects of ACE inhibition have important clinical implications. In patients with hypertension who have no detectable obstruction of renal blood flow, ACE inhibition reduces blood pressure while increasing renal blood flow[7,10] and maintaining or improving glomerular filtration rate. However, in patients with renal artery stenosis, the situation is different.[7] Because of the stenosis, renal perfusion pressure is reduced. Therefore, in both animals and humans, ACE inhibition and the subsequent depletion of available angiotensin II lead to a decrease or even a cessation of glomerular filtration beyond the stenosis.

The renovascular effects of quinapril have been demonstrated in studies that included measurement of creatinine clearance or serum creatinine and serum urea levels. In 1 study of 20 hypertensive patients, quinapril (20 mg once daily) was administered for 7 days. Patients were stratified, with 5 patients in each group, according to creatinine clearance rates of >90, 61–90, 31–60, and <31 mL/min.[11] In no group did the 7-day regimen of quinapril affect serum levels of either urea or creatinine.

In another study of 22 hypertensive patients, 17 of whom completed the trial and were evaluated, quinapril was administered on day 1 (20 mg once daily), and subsequently on each day of days 4 through 10. Patients were stratified according to creatinine clearance rates: >60 (4), 30–59 (5), and <30 mL/min (8). The average creatinine clearance values for each group before treatment were 105, 44, and 16 mL/min, respectively. At the end of the treatment period these values were 96, 48, and 20 mL/min.[11]

TABLE I Beneficial Renal Responses to Interruption of the Renin-Angiotensin-Aldosterone Axis in Primary Essential Hypertension

Reduction of renal vascular resistance
Enhancement of renal blood flow
Enhancement of glomerular filtration rate
Acute natriuresis
Increase in free water clearance
Spared potassium loss
Decrease in urinary protein excretion

Reproduced with permission from Bauer and Reams.[8]

In comparative studies of enalapril and quinapril, the proportion of patients with high serum creatinine values was similar for once- and twice-daily enalapril (5 and 8%, respectively) and twice-daily quinapril (6%), but the incidence decreased to 1% with once-daily quinapril. To explain these findings, it was suggested that once-daily quinapril allowed restoration of glomerular filtration pressure (and reversal of any renal hypotensive effect) toward the end of the dosing interval, while maintaining blood pressure control.[12]

Since elevated baseline serum creatinine concentration has been demonstrated to be a strong independent risk factor for mortality in hypertensive patients, these findings may have broader clinical implications.[13]

HEPATIC BLOOD FLOW

Although ACE inhibitors increase renal blood flow, they appear to cause a reduction or no change in hepatic blood flow. Some clinical and experimental studies have demonstrated that the reduction in total systemic resistance with the ACE inhibitor captopril is associated with an increase in renal blood flow without any arteriolar

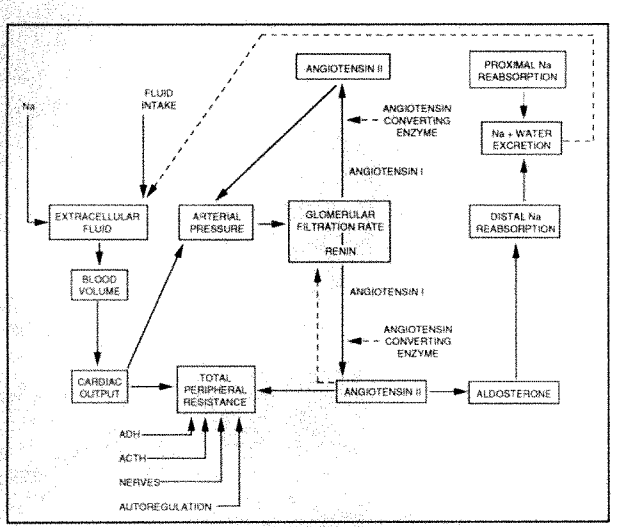


FIGURE 1. The renin–angiotensin system and the feedback mechanism in hypertension. (From Rosenfeld and Zabludowski.[4]) ACTH = adrenocortic tropic hormone; ADH = antidiuretic hormone; Na = sodium.

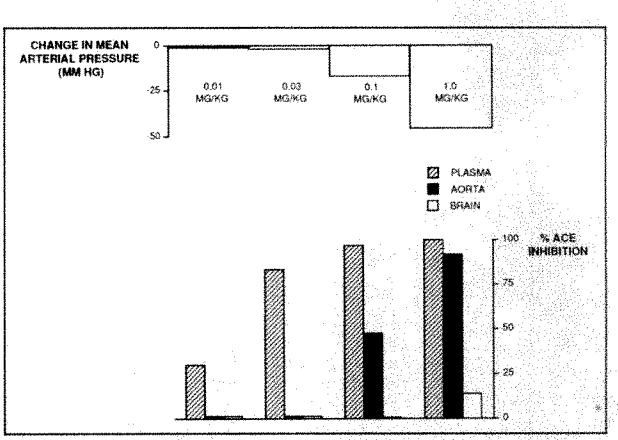


FIGURE 2. Relation between mean arterial blood pressure reduction and angiotensin-converting enzyme (ACE) inhibition with quinapril in renal hypertensive rats (n = 4). (From Kaplan et al.[5])

dilatation in splanchnic or musculoskeletal beds, suggesting that selective vasodilatation occurs in different regional vascular beds.[14]

Crossley et al[14] studied the acute effects of captopril on hepatic blood flow and systemic hemodynamics in 6 patients with essential hypertension. Mean arterial pressure decreased from 141.9 ± 6.9 to 130.2 ± 6.7 mm Hg ($p < 0.05$) 1 hour after the administration of captopril. There was no significant change in other hemodynamic values, but hepatic blood flow decreased uniformly from 1,127 ± 115 to 841 ± 93 mL/min ($p < 0.001$).

Eriksson et al[15] reported somewhat different results. This group examined the possible contribution of the renin–angiotensin–aldosterone system to portal hypertension in patients with cirrhosis of the liver. Hepatic venous wedge pressure was 22 ± 2 mm Hg in the basal state and decreased to 19–20 mm Hg at 45–90 minutes after the administration of captopril ($p < 0.05$–0.01).

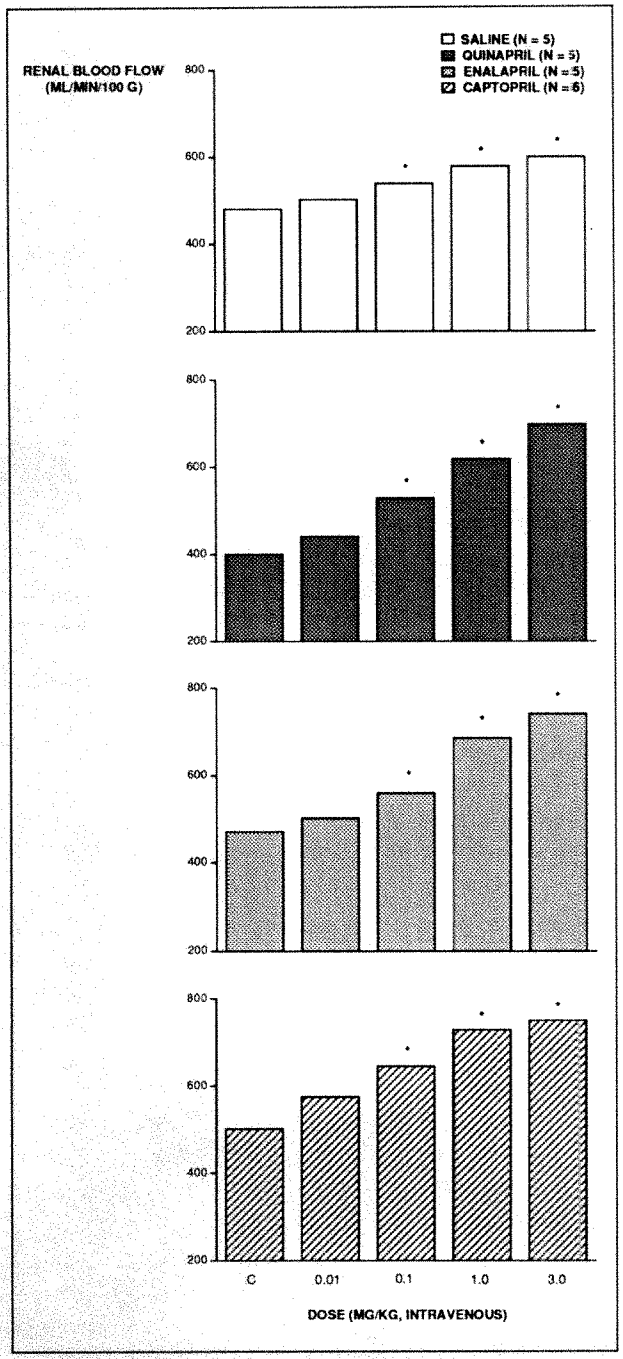


FIGURE 3. Effects of quinapril, captopril, enalapril, and saline (3 ml/dose) on renal blood flow in anesthetized dogs; *p >0.05 vs control. C = control. (From Kaplan et al.[5])

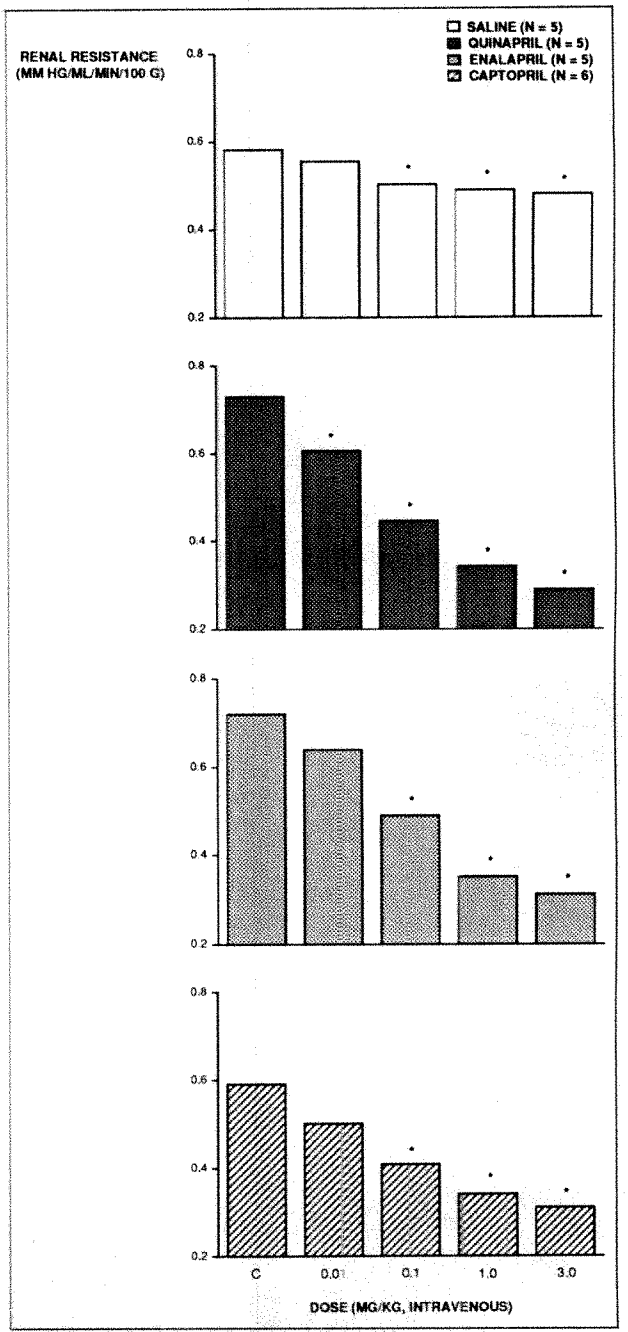


FIGURE 4. Effects of quinapril, captopril, enalapril, and saline (3 ml/dose) on calculated renal vascular resistance in anesthetized dogs. *p >0.05 vs control. C = control. (From Kaplan et al.[5])

The difference in wedge-to-free hepatic venous pressure (basal 14 ± 2 mm Hg) remained unchanged after captopril, and estimated hepatic blood flow was unaltered.

Despite the significant reduction or lack of change in hepatic blood flow reported by some investigators, ACE inhibition is associated with reduced splanchnic vascular resistance. Ventura et al[16] observed a reduction in resistance in the splanchnic vasculature in 11 patients with mild to moderate essential hypertension immediately after oral administration of 25 mg of captopril. Such findings may have important clinical implications.

LIMB (PERIPHERAL) BLOOD FLOW

Since changes in vascular resistance can be assessed indirectly by measurement of limb blood flow, investigators have found it appropriate to assess the effects of different antihypertensive agents on limb blood flow and vascular resistance during treatment.[17] These measurements may also be useful in predicting the effects of antihypertensive agents on the lower limb circulation in patients with hypertension complicated by peripheral vascular disease.

ACE inhibitors reduce total peripheral resistance and maintain or somewhat reduce limb blood flow. Roberts et al[17] found that despite differing modes of action, 4 different drugs (atenolol, labetalol, pindolol, and captopril) reduced limb blood flow. The investigators attributed this primarily to reduced perfusion pressure associated with limited autoregulation of skeletal muscle circulation.

SKELETAL AND CUTANEOUS PERFUSION

ACE inhibition has also been found to augment skeletal flow in normal subjects. Ventura et al[16] observed an immediate increase in blood flow to skeletal muscle and skin, as well as a reduction in vascular resistance in the vessels supplying these areas in patients treated with 25 mg of captopril. Long-term treatment (8 weeks) with captopril has also been found to increase skeletal muscle blood flow both at rest and during exercise as determined by the Xenon method.[18] Moreover, long-term ACE inhibition appeared to improve exercise tolerance primarily in those patients in whom peak skeletal muscle blood flow was augmented. Several factors, such as reduction in plasma and vascular angiotensin II and sympathetic nervous activity, and increased prostaglandin levels and renal function, may contribute to this beneficial long-term effect.[18]

BRACHIAL ARTERY FLOW

The arterial effects of acute ACE inhibition are not restricted to the arterioles but also involve the large arteries.[19] Indeed, many studies have demonstrated an increase in brachial artery flow with ACE inhibitors.[2,20] Vasodilatation in this region is not unexpected, since other vasodilators appear to have a primary action on muscle flow.[2]

Faxon et al[2] found that after ACE inhibition, forearm blood flow significantly increased in normal subjects (2.8 ± 0.8 to 5.9 ± 1.0 mL/100 g; $p \leq 0.02$). Forearm vascular resistance also decreased in normal volunteers. Ventura et al[16] reported similar findings in patients with mild to moderate essential hypertension.

In 1983, Simon et al[19,21-23] demonstrated the dilator effect of ACE inhibition on large arteries.[22] In short-term investigations in patients with sustained essential hypertension, the investigators reported that, with a slight decrease in blood pressure, the brachial artery diameter increased markedly. Thus, it was shown that in addition to the more classic dilating effect on small arteries, ACE inhibition has a direct dilating effect on the intact large arteries.

Simon et al[21] also examined the effect of captopril on large arteries in men with sustained essential hypertension. After captopril administration, a 20% increase in arterial compliance was observed. The same increase was obtained with a 5% (acute experiment) and 15% (short-term experiment) decrease in blood pressure, indicating that the decrease in pressure could not explain exclusively the increase in compliance. This assumption was studied with determinations of brachial artery diameter using original pulsed Doppler systems. After captopril administration, brachial artery diameter increased markedly despite the decrease in blood pressure. The investigators concluded, therefore, that in addition to its effect on small arteries, captopril also has an effect on the large arteries of patients with essential hypertension.

In patients with uncomplicated essential hypertension, short- or long-term ACE inhibition was accompanied by a significant increase in arterial compliance and dilation of the brachial artery.[19] The investigators related this response to changes in plasma or intraarterial angiotensin or to changes in plasma potassium, or a combination of these.

The beneficial effect of ACE inhibition on the large arteries has also been shown to persist over long-term treatment. In a double-blind study, Simon et al[22] compared forearm arterial hemodynamics after enalapril and propranolol over a 6-month period. For the same decrease in blood pressure, propranolol did not change the brachial hemodynamic indices whereas enalapril improved them. Arterial diameter and blood flow velocity increased, causing a significant elevation in brachial blood flow. Furthermore, arterial compliance increased. The increase in arterial compliance was more pronounced with enalapril than with propranolol, which caused the same decrease in blood pressure. The results of the studies by Simon et al suggest that ACE inhibition

TABLE II Desirable Regional Hemodynamic Effects of ACE Inhibition

Increased renal blood flow
Enhanced glomerular filtration rate
Increased limb blood flow
Increased skeletal blood flow
Increased cutaneous blood flow
Dilatation of the large arteries (e.g., brachial)
Maintenance of cerebral blood flow

ACE = angiotensin-converting enzyme.

was directly responsible for the improvement in the viscoelastic properties of large arteries in treated hypertensive patients.

Based on the results of their studies, Simon et al concluded that ACE inhibition, whether in short- or long-term treatment, may reverse the functional alteration (reduced arterial compliance) of large arteries (e.g., brachial) in patients with essential hypertension.[19,22]

CEREBRAL BLOOD FLOW

Both animal and human studies have demonstrated that ACE inhibitors can safely reduce blood pressure without impairing cerebral blood flow. Barry et al[24] examined the cerebrovascular effects of the ACE inhibitor captopril in normotensive and hypertensive rats. Cerebral blood flow was measured with the intracarotid ^{133}Xe injection method in halothane-anesthetized animals. The blood–brain barrier permeability of captopril (determined with an integral-uptake method) was negligible. When administered into the cerebral ventricles to bypass the blood–brain barrier, captopril had no effect on cerebral blood flow. Furthermore, cerebral blood flow autoregulation (studied by increasing and decreasing blood pressure) was identical to that in control subjects.

In humans, captopril keeps regional cerebral blood flow constant even with lower blood pressure values.[25] Similar results have been reported with enalapril. Frei and Müller-Brand[26] studied regional cerebral blood flow with the intravenous ^{133}Xe method in 20 patients with moderate hypertension. All patients received placebo followed by 2 months of therapy with enalapril. Despite a significant reduction in blood pressure, regional cerebral blood flow was not impaired by enalapril.

The means by which ACE inhibitors maintain regional cerebral blood flow during reduced blood pressure levels is uncertain. ACE in the brain is found on both sides of the blood–brain barrier; it occurs on the luminal endothelium membrane of cerebral vessels and within the brain.[24]

Some ACE inhibitors penetrate the blood–brain barrier if administered in high doses. Oral gavage with perindopril 16–32 mg/kg reduced brain ACE activity,[27] whereas increasing doses of perindopril progressively inhibited ACE activity in rat caudate putamen and globus pallidus.[28] Cohen and Kurz[29] reported similar data for enalapril, showing a dose-proportional inhibition of brain enzyme in rats. However, oral administration of either 0.1 or 1.0 mg/kg of quinapril to rats failed to inhibit brain ACE, although plasma and aortic ACE were inhibited.[30] The lack of effect of quinapril on brain ACE activity was also confirmed by Johnston et al,[28] using a similar animal model. After administration of [^{14}C]quinapril to rats, radiolabel was distributed rapidly and extensively to all tissues except brain.[11] It was likewise reported that radiolabeled captopril did not penetrate the central nervous system in rats.[31]

Therefore, ACE inhibitors differ in their ability to penetrate different tissues and to bind to tissue ACE. These properties may depend on the polarity or lipophilicity of an inhibitor. Such differences are likely to be reflected in differences in clinical efficacy. Indeed, both quinapril and quinaprilat have lower IC_{50} values for ACE inhibition than captopril,[30] and administration of 1.0 mg/kg of quinapril to hypertensive rats caused nearly complete inhibition of both plasma and aortic ACE activity, but reduced brain ACE activity by <15%.[30] Cohen and Kurz[29] showed that 10 mg/kg captopril was required to achieve similar inhibition of aortic and plasma ACE in spontaneously hypertensive rats, but it also produced a 73.7% reduction in brain ACE activity.

CONCLUSION

Since an increase in total vascular resistance is the primary hemodynamic disturbance of essential hypertension, the ideal antihypertensive agent would lower blood pressure lvvels while also reducing vascular resistance. ACE inhibitors have been shown to fulfill these requirements. Hemodynamically, all ACE inhibitors act as vasodilators. Desirable regional hemodynamic effects include increased renal, limb, and skeletal perfusion, dilation of the large arteries such as the brachial artery, and maintenance of cerebral blood flow during blood pressure reduction (Table II).

Although the precise mechanism for increasing blood flow to local tissues is not clear, the effects of ACE inhibition on local renin–angiotensin systems clearly play an important role. Both animal and human data suggest that the principal action of ACE inhibitors, and particularly of quinapril, occurs at local tissue sites. This may help explain the beneficial effects at the specific tissues affected by hypertensive disease (renal, hepatic, limb, skeletal, brachial, and cerebral tissues), and some of these effects may have even broader clinical implications. It is also possible that different ACE inhibitors may have differential effects on individual tissue ACE with variable bioavailability in different organs. Thus, additional

TABLE III Potential Advantages of New ACE Inhibitors (e.g., Quinapril)
Enhanced bioavailability in certain organs Greater potency in local tissues Greater distribution in local tissues Longer duration of action in local tissues
ACE = angiotensin-converting enzyme.

effects at tissue sites may be influenced by certain unique structural properties of the individual ACE inhibitors. Some agents (e.g., quinapril) may prove to have greater potency, distribution, or duration of action in local tissues, providing even more desirable regional hemodynamic effects (Table III) and additional benefits for patients suffering from hypertension.

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Adverse Effects of Angiotensin-Converting Enzyme Inhibitors in Antihypertensive Therapy with Focus on Quinapril

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Angiotensin-converting enzyme (ACE) inhibitors are useful first-line drugs in the therapy of mild and moderate hypertension. Adverse reactions to this drug class are rarely serious. Hypotension, cough, rash, and taste disturbance are uncommon; reduced glomerular filtration and hyperkalemia occur infrequently; angioedema is rare and neutropenia is extremely rare.

Quinapril is a new ACE inhibitor that is converted to biologically active quinaprilat in the liver. This ACE inhibitor has a rapid onset of action and inhibits local tissue converting enzyme systems in kidney, heart, and brain, as well as in the circulating renin–angiotensin system. Clinically significant adverse effects of quinapril occur at low rates. In 1,771 patients receiving quinapril, the reported incidence of the first occurrence of orthostatic hypotension was comparable to that seen in patients receiving placebo. In other studies, headache was reported by up to 4.7% of patients receiving quinapril, which is comparable to reported incidences of headache in patients receiving other ACE inhibitors. Other adverse events reported at rates >1% include cough with associated rhinitis and bronchitis, dizziness, and somnolence. Such adverse events have only rarely led to the withdrawal of patients from clinical studies of quinapril.

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Clinical experience over the past decade has shown that angiotensin-converting enzyme (ACE) inhibitors are as effective as older drugs in lowering blood pressure, are associated with fewer symptomatic side effects, and produce little change in laboratory parameters. In addition, they appear to possess both renal and cardioprotective properties. The serious adverse reactions reported from early uncontrolled experience with captopril, the prototype drug, are rarely reported today. The early use of captopril in doses up to 1,200 mg daily was mostly limited to severely hypertensive patients, many of whom had underlying diseases such as systemic lupus erythematosus and progressive systemic sclerosis.[1] The Veterans Administration Cooperative Study Group on Antihypertensive Agents conducted a prospective double-blind study to determine whether much lower doses of captopril would be effective and safe in a population of patients with mild to moderate hypertension. This study demonstrated that as little as 37.5 mg of captopril/day was as effective as 150 mg/day in this mildly hypertensive population and that the safety profile was excellent.[2,3] In recognition of this and other favorable experience, the 1988 Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure[4] upgraded ACE inhibitors to first-line therapy along with diuretics, β blockers, and calcium antagonists.

PHARMACOLOGY OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Mechanism of action: Although the mechanisms of action of ACE inhibitors have not been fully elucidated, their major foci involve both the endocrine renin–angiotensin–aldosterone system and paracrine and autocrine (tissue and cellular) vasoactive substances.[5,6] Renin acts enzymatically on the substrate angiotensinogen to form the decapeptide angiotensin I, which in turn is cleaved by ACE into the octapeptide angiotensin II, a potent direct vasopressor and stimulant for aldosterone release.

ACE inhibitors act at the tissue and cellular level by blocking the generation of angiotensin II,[5,6] increasing tissue levels of bradykinin, and directly or indirectly stimulating the synthesis of prostaglandin and prostacyclin.[7] This action is of particular importance in the kidney vasculature (both arteries and veins), as well as in the heart and brain.[8,9] Astrocytes have been identified as the source of angiotensinogen in the brain.[10]

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Early data suggested that ACE inhibitors were more effective in patients with high plasma renin activity than in those with low plasma renin activity. It soon became apparent, however, that they could be effective even in patients with low plasma renin activity, such as many black or elderly patients.[11] These data drew attention also to the importance of distinguishing between groups of patients when considering the relative efficacy of ACE inhibitors: these drugs are usually more effective in young patients than in old, and more effective in whites than in blacks. Combination of a thiazide diuretic with an ACE inhibitor abolishes these race and age differences.[12]

Inhibition of both plasma and aortic ACE activity has been demonstrated in renal hypertensive rats treated orally with doses of 0.01–1 mg/kg of quinapril. As may be the case with other ACE inhibitors, the antihypertensive activity of the drug, however, correlates poorly with plasma ACE inhibition. A much better relation is apparent between the blood pressure-lowering effect of quinapril and aortic ACE inhibition, suggesting that vascular tissue ACE inhibition may be more important than plasma ACE inhibition in the antihypertensive effect and overall clinical profile of these drugs.[13]

Biochemistry: Captopril, the original orally active ACE inhibitor, is derived from the amino acid proline (Figure 1), as are most newer agents.[14] Because some of the side effects of captopril were originally attributed to its sulfhydryl group, new drugs without such a group were prepared and tested.[15] Enalapril, ramipril, cilazapril, and quinapril are prodrugs that are hydrolyzed in the liver to their pharmacologically active diacid metabolites, enalaprilat, ramiprilat, cilazaprilat, and quinaprilat, respectively. Lisinopril, a lysine analog of enalapril, does not require hepatic activation, has a slow onset of action, and is very long-acting. On the other hand, quinapril is also long-acting but has a rapid onset of action: significant reductions in plasma ACE activity are achieved within 1 hour of quinapril dosing, and peak plasma concentrations of quinaprilat occur within 2 hours of administration.[16]

SIDE EFFECTS

Clinical experience with ACE inhibitors has led to the recognition that adverse effects are few and relatively mild; they lead to discontinuation of the drug in <5% of the patients who receive them for hypertension. Nevertheless, there are adverse effects that need to be recognized and dealt with appropriately. Many of them can be avoided altogether.

An incorrect assumption that some or all of the adverse effects related to captopril were due to the presence of a mercapto group ($HSCH_2^-$), especially the sulfhydryl (−SH) moiety, led to the development of a large number of compounds that did not have a sulfhydryl group. The first of these was enalapril.[17] Subsequent experience has suggested that there may be some minor differences in the frequency of specific adverse effects between the various ACE inhibitors, but this has never been documented to be due to the sulfhydryl group.

The potential adverse effects of ACE inhibitors are detailed with particular attention to their avoidance as well as their management.

Hematologic effects: Although very rare, hematologic adverse effects associated with ACE inhibitors are the most serious.[18,19] The most common problem is neutropenia, which tends to occur in the first 3 months of treatment. Aplastic anemia is extremely rare; a few deaths have been reported, all associated with underlying disease. As previously mentioned, the high doses of captopril used in the uncontrolled treatment of seriously ill patients, some of whom were being treated with immunosuppressive agents or who had diseases that have associated hematologic abnormalities, have confounded the literature. Further complicating the problem is the observation of spontaneous neutropenia in perfectly healthy people who are black or of Mediterranean origin, benign cyclic neutropenia, and the neutropenia that can be associated with ethanol ingestion.[20] Cooper[21] has reviewed this issue and put it into perspective. In a database of >6,000 patients treated with captopril, only 83 were

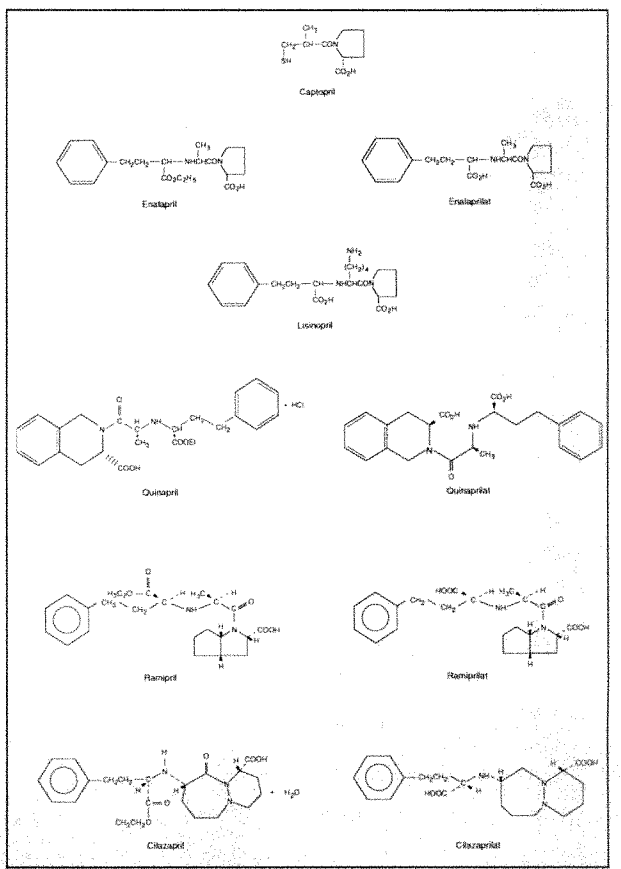


FIGURE 1. Chemical structures of angiotensin-converting enzyme inhibitors.

found with identifiable neutropenia. Of these, 39 failed to meet the criteria for captopril association mostly because of the concomitant use of cytotoxic agents. The 44 patients who were considered to have captopril-associated neutropenia were characterized by renal failure in 36 (11 required maintenance hemodialysis) and by systemic lupus erythematosus or progressive systemic sclerosis (scleroderma) in 13. Only 1 patient (0.02%) with normal renal function and no collagen vascular disease had neutropenia. This is comparable to many commonly used drugs, including the phenothiazines. In the group of patients who had a serum creatinine ≥2.0 mg/dL, the incidence of neutropenia was 0.40%, and it was 7.2% for those patients who had both serum creatinine ≥2.0 mg/dL and either lupus or progressive systemic sclerosis. In most of the cases, neutropenia was the only hematologic abnormality, but the more serious cases had thrombocytopenia and evidence of erythropoietic suppression as well. Fortunately, most of the neutrophil counts returned to normal after discontinuation of captopril and some remained normal even after captopril was restarted.

Leukopenia (<3,000 white blood cells/mm^3) has been rare (0.5%) in patients receiving enalapril, and agranulocytosis and infection have not been ascribed to its use.[22,23]

Available data for quinapril thus far attest to its relatively mild effect on bone marrow. No drug-related neutropenia (<1,500 polymorphs/mm^3) or agranulocytosis (<2,000 white blood cells/mm^3) occurred in patients who received quinapril in clinical trials, and none showed clinical evidence of neutropenia or myelosuppression.[24,25] Further follow-up revealed that a slight reduction in white blood cell count occurred in 0.4% of 1,600 patients and of neutrophils in 2.5% of 1,417 patients. In general, counts returned to normal during continued therapy.

There have been no reports of hematologic toxicity associated with lisinopril.[26] Hemoglobin levels decreased in 1 patient but returned to baseline values within 2 months of treatment discontinuation, whereas hemoglobin returned to baseline levels in 3 patients who continued therapy. No leukopenia or thrombocytopenia was seen. In a comparative study of ramipril (n = 129) and captopril (n = 119), no clinically relevant hematologic abnormalities were found with either group.[27]

How then should the clinician deal with the issue of neutropenia associated with ACE inhibitors? I believe that the answer is very simple. If the patient has a serum creatinine level <2.0 mg/dL, no additional laboratory work is needed. The incidence of neutropenia is so vanishingly low that serial complete blood cell counts are useless. Patients should have the same basic laboratory workup (including a complete blood cell count) that would be done for any routine hypertension patient irrespective of the planned drug therapy. If, however, the patient has a serum creatinine ≥2.0 mg/dL, then the clinician should exercise care to keep the dose of the drug as low as possible and to instruct the patient to call at the first sign of a sore throat. These patients tend to be monitored more frequently because of their underlying illness; routine complete blood cell counts are still unwarranted. The vast majority of the sore throats will be due to causes other than neutropenia. ACE inhibitors may be lifesaving for patients with renal failure plus a collagen vascular disease. With intensive treatment, the life expectancy for patients with scleroderma renal crisis has increased from an average of 23 days to many years.[28] The risk of 7.2% neutropenia in a disease with a 93% mortality at 1 year if untreated seems well warranted. In summary, the problem of ACE inhibitor-associated neutropenia is a non-problem for the vast majority of patients and those at risk can be easily identified and monitored appropriately.

Proteinuria: The issue of proteinuria putatively associated with ACE inhibitors is particularly vexing not only because it is based on erroneous data, but because ACE inhibitors are of particular value in patients with proteinuria.[28] Once again, the early uncontrolled use of captopril in seriously ill patients led to the incorrect assumption that captopril was responsible for proteinuria. This was compounded by the logical quantum leap to the conclusion that captopril was chemically similar to penicillamine, a compound known to cause proteinuria. This topic has been carefully reviewed by Lewis,[29] who pointed out the frequency of proteinuria in the hypertensive population and the extreme difficulty in proving causality between any ACE inhibitor and the development of proteinuria. Membranous glomerulopathy is common and may present with hypertension without clinically important urinary abnormalities. These patients may pass the placebo washout phase of a controlled trial only to exhibit proteinuria after the study drug is started. Two of our patients in the Veterans Administration cooperative study on low-dose captopril[3] developed proteinuria while taking placebo. In a trial we conducted with enalapril in which two 24-hour urine collections were required during the placebo washout phase, a male patient had <150 mg in the first sample and over 8,000 mg in the second! Had the patient received enalapril before the second collection, the patient would have been erroneously classified as having enalapril-associated proteinuria.

Six (0.66%) of 915 hypertensive patients from whom 24-hour urine samples were collected during enalapril phase III clinical trials exhibited slight transient elevations in urinary protein values, but none developed the nephrotic syndrome or glomerulonephropathy.[22] Data from 660 patients who received lisinopril in hypertension trials showed that 3 (0.5%) had urinary protein losses >1 g/day.[26] Two of these patients had minor proteinuria

(1.5 g/day) and were permitted to continue therapy, whereas the third had entered the study with elevated urinary albumin values. Four patients (0.1%) of 3,031 receiving quinapril in clinical trials had clinically unimportant proteinuria; none had serious renal impairment.[25] In a total of 248 patients treated in a multicenter study with either captopril (50 mg twice daily) or ramipril (10 mg once daily), no case of proteinuria was reported,[27] whereas 0.6% of patients (n = 3,769) receiving cilazapril were found to have proteinuria.[30]

What should the clinician do about the issue of proteinuria? I believe strongly that this is a non-issue. All hypertensive patients should have a urine dipstick test as part of their routine workup. If the protein indicator records ≥1+ concentration of protein, a 24-hour urine collection for protein should be performed. This should serve to identify those patients with baseline intrinsic renal disease. Further workup should be done as clinically indicated. The presence of proteinuria is not a contraindication to the use of an ACE inhibitor. Indeed, given that angiotensin II promotes proteinuria (as does hypertension, per se), this may actually be an indication for the use of an ACE inhibitor.

Renal function: ACE inhibitors have different effects on renal function in different clinical settings. Angiotensin II is 1 of the normal mediators of glomerular filtration rate. It helps to control the tone of the efferent arterioles and is capable of causing mesangial cell contraction. Maintenance of glomerular filtration rate during states of volume depletion (or distal to a stenotic lesion of a renal artery or in the reduction of effective intraarterial volume in patients with congestive heart failure) is a function of angiotensin II that is interdicted by ACE inhibitors. The net result in the aforementioned settings could be reduction of glomerular filtration rate. This readily explains the mechanism for the elevation in serum creatinine when patients are overdiuresed or become dehydrated when taking ACE inhibitors and when ACE inhibitors are used to treat patients with severe congestive heart failure, especially if they are taking diuretics. It also explains the phenomenon of reversible renal failure seen in patients with bilateral renal artery stenosis or stenosis of an artery supplying a solitary kidney (e.g., a renal transplant).[31,32]

Most problems with decreased renal function associated with ACE inhibitor therapy occur during the treatment of congestive heart failure. The basic problem is failure of the left ventricle to pump an adequate pressure head to the kidneys. Plasma renin activity tends to be very high (as are norepinephrine, antidiuretic hormone, and other vasoactive substances); low serum sodium may reflect very high plasma renin activity and provides warning to the clinician that the patient may be particularly susceptible to both decreased glomerular filtration rate and hypotension after administration of an ACE inhibitor.[33] These problems can be avoided or mitigated by recognizing the patient at risk. Those patients should receive very small initial doses of a short-acting ACE inhibitor (i.e., ≤6.25 mg of captopril). The patients should not be overdiuresed. Indeed, it is not necessary to dry the lungs completely. Functional status of the patient is the main guideline. The adverse effects of enalapril on glomerular filtration rate compared to captopril in the study of Packer et al[34] of patients with congestive heart failure may have been due to too high a dose of enalapril. Treatment with enalapril caused a reduction of endogenous creatinine clearance from 54.1 ± 6.1 to 44.1 ± 5.3 mL/min compared to 49.2 ± 4.7 to 55.2 ± 6.8 mL/min with captopril ($p < 0.05$).

In general, there is no significant worsening of renal function of hypertensive patients who are treated with ACE inhibitors. Many hypertensive patients who exhibit abnormal renal blood flow responses to sodium load (non-modulators) seem to benefit particularly from ACE inhibition.[35] ACE inhibitors may also be of special benefit in protecting against progression to end-stage renal disease, particularly in diabetic hypertensives.[36]

In a group of 586 hypertensive patients, Frank[37] found that twice-daily dosing with quinapril or enalapril resulted in elevated serum creatinine levels in 6 and 8% of patients, respectively. On the other hand, with once-daily dosing in hypertensive patients, elevated serum creatinine levels were seen in 1% of quinapril patients and in 5% of enalapril patients. Frank hypothesized that once-daily quinapril allowed restoration of glomerular filtration pressure before administration of the next scheduled dose.[37]

When an ACE inhibitor is associated with acute deterioration of renal function in a hypertensive patient, the ACE inhibitor should be discontinued. If the serum creatinine levels return to baseline in 7–10 days (the baseline is usually elevated to >2.0 mg/dL in these patients), then a presumptive diagnosis of renal artery stenosis should be made and the appropriate steps toward diagnosis and definitive therapy taken. Decreased renal function in the hypertensive patient is not a contraindication to the use of ACE inhibitors, although the dose should be kept as low as possible.

Dermatologic effects: Captopril may be associated with a maculopapular (but rarely urticarial) rash with or without pruritus in the first 4 weeks of therapy.[38] Rash is accompanied rarely by fever, arthralgia, and eosinophilia. In general, it tends to be mild, usually responds to dosage reduction or a short course of antihistamines, and may resolve spontaneously even if captopril therapy is continued. The incidence is in the range of 4–7% and correlates with renal status (because of the effect on plasma concentration) as well as with captopril dose.

Analysis of data from controlled clinical trials showed skin rash to be present in 1.4% of 2,314 patients receiving enalapril for hypertension.[38] Rash was reported by 1.5% of 2,003 patients receiving lisinopril for hypertension or congestive heart failure in clinical trials.[38] Combined data from comparative trials for hypertension and congestive heart failure show an incidence of 0.2% in 1,491 patients receiving quinapril, 0.3% of 339 patients receiving enalapril, and 2.2% of 186 patients receiving captopril, compared with no rash in 74 patients receiving chlorthalidone and 394 patients receiving placebo.[24]

Dysgeusia: Loss or alteration of taste occurs in 2–4% of patients receiving captopril, depending on dose and renal status.[38] Dysgeusia tends to be self-limited and reversible in 2–3 months even if the drug is continued, although patients may lose weight as a result. Henkin[39] speculates that since captopril binds to the zinc site of the converting enzyme (a metalloenzyme), it can also inhibit the zinc metalloenzyme gustin, which is intimately involved in taste. Of patients receiving enalapril, <1% have experienced this side effect.[22,23,38] In clinical trials of quinapril, 0.3% experienced taste loss and 0.3% reported unusual taste.[25] In a study of 83 elderly patients with essential hypertension, treatment with cilazapril was not associated with any report of taste disturbances.[30]

Cough: An adverse reaction that seems to be a class effect of ACE inhibitors is a dry cough, accompanied by tickling in the throat, sometimes with nasal stuffiness and wheezing.[40–46] The mechanism has not been established but may be related to increased bradykinin levels, or perhaps to an effect on vagal nerves.[46] In interviews of patients receiving various ACE inhibitors, Goldszer et al[43] did not note statistically significant differences in the prevalence of cough among those receiving captopril (11.5%), cilazapril (13.3%), or enalapril (24.7%). The incidence of cough in 3,031 patients (84% with hypertension) treated with quinapril in clinical trials was 8.3% and that for rhinitis was also 8.3%.[25]

Angioedema: Angioedema is another class effect (possibly involving bradykinin release) that may develop in patients treated with ACE inhibitors.[43] Although rare, angioedema is potentially dangerous because asphyxiation may result if the tongue, glottis, or larynx is affected. Incidence rates of ≤0.1% have been reported for captopril,[38] lisinopril,[38] and quinapril,[25] compared to about 0.2% for enalapril.[38]

Hyperkalemia: ACE inhibitors do not derange the metabolism of uric acid, calcium, glucose, triglycerides, or cholesterol. However, their ability to decrease aldosterone secretion may result in minor elevations of serum potassium. A potential for hyperkalemia exists in patients receiving potassium-sparing diuretics, severe salt restriction, or nonsteroidal anti-inflammatory drugs, as well as in those with congestive heart failure, low glomerular filtration rate, or diabetes mellitus.[46] Potassium-sparing diuretics and oral potassium supplements should be avoided or used very carefully because their hyperkalemic effects may be additive with those of ACE inhibitors.

Hypotension and orthostatic hypotension: Besides the elderly, who may be vulnerable to hypotension because of the age-related decline in baroreceptor responses, other patients at special risk include those already receiving diuretics or sodium-restricted diets.[46] In overdiuresed patients and in hypertensive patients with endogenous high plasma renin activity, excessive blood pressure reduction in response to converting enzyme inhibition may result in first-dose hypotension and underperfusion of the kidneys. This adverse effect may be minimized or avoided altogether by discontinuing the diuretic or by increasing salt intake before institution of ACE inhibitor therapy and by administering small test doses to patients in whom high plasma renin activity or renal impairment is suspected.

A postmarketing surveillance review in 1985 indicated that transient symptoms of hypotension (dizziness, lightheadedness, vertigo) were reported by 5.0% of captopril-treated patients independent of their dose or their renal function status.[47] Among those treated with captopril for congestive heart failure, 3.6% withdrew because of hypotension.[38] Hypotension occurred in 0.9% of patients receiving enalapril for hypertension and 0.5% experienced orthostatic effects.[38] Lisinopril monotherapy has produced hypotension in 1.8% of patients treated for hypertension or congestive heart failure and orthostatic effects in 1.4% (discontinuation rates for these adverse reactions were 0.8 and 0.0%, respectively).[38] For quinapril the combined incidence of hypotension and orthostatic effects has been approximately 1% in patients treated for hypertension and about 2% in patients treated for congestive heart failure.[25]

The first occurrences of hypotension and orthostatic hypotension (events were counted separately when they appeared in the same patient and were further segregated into symptomatic or asymptomatic) in controlled, double-blind clinical trials of quinapril are summarized in Table I. The incidence of these events was smaller with quinapril than with enalapril or captopril.[24]

The incidence of a first-dose hypotensive effect from quinapril was explored in double-blind studies of 971 patients who received quinapril and 230 who received placebo.[25] It occurred in 1.6–2.5% of patients receiving a range of doses of quinapril alone, in 4.8% of those receiving a concomitant diuretic, and in 3.9% of patients receiving placebo. The incidence in quinapril-treated patients was low and comparable to that with placebo.

DRUG INTERACTIONS

At least 1 drug interaction involving ACE inhibitors may be beneficial: they tend to blunt the hypokalemia induced by thiazide diuretics.[4] On the other hand, nonsteroidal anti-inflammatory drugs, including aspirin, may amplify their tendency to retain potassium. As pointed out earlier, use of potassium-sparing diuretics or oral potassium supplements should be avoided in patients receiving an ACE inhibitor because the risk of hyperkalemia is magnified. Moreover, ACE inhibitors should be introduced cautiously in patients already receiving diuretic therapy because renin levels tend to be increased by drug-induced natriuresis, predisposing patients to first-dose hypotension.

OVERDOSE

Little is known about the consequences of ACE inhibitor overdose. A review of published reports found 3 cases of attempted suicide with excessive doses of ACE inhibitors. All 3 efforts failed; the only adverse effect was hypotension that responded to intravenous fluids.

COMPARISONS WITH OTHER DRUG CLASSES

Although drug therapy has had a considerable impact on controlling high blood pressure, the dropout rates in large hypertension trials have been high because of adverse effects—i.e., ≥16% of those entering—while for those remaining, the price may be a significant diminution in overall quality of life because of subtler effects on mood, energy level, sleep quality, and sexual function.[48,49] For example, in a double-blind multicenter study to determine the influence of antihypertensive drugs on quality of life in 626 men with mild to moderate hypertension, Croog et al[50] compared not only the efficacy and incidence of side effects but the impact on quality of life of 3 major antihypertensive agents. They reported a lower dropout rate because of adverse experiences in patients treated for 24 weeks with captopril (8%) than with propranolol (13%) or methyldopa (20%). The difference between captopril and methyldopa was statistically significant ($p = 0.001$) and that between methyldopa and propranolol approached significance ($p = 0.058$). In this study there were significantly ($p < 0.05$ to < 0.01) more favorable changes from baseline in general well-being, physical symptoms, work performance, life satisfaction, and cognitive function among patients randomized to captopril than in those receiving methyldopa. Compared with the propranolol group, the captopril group had significantly ($p < 0.05$ to < 0.01) more positive changes in general well-being, physical symptoms, and sexual dysfunction. Moreover, 20% more patients taking methyldopa and 15% more patients taking propranolol experienced worsening of general well-being than did patients in the captopril group. Compared with those taking captopril, significantly more patients receiving methyldopa had fatigue, dry mouth, and blurred vision, and significantly more patients receiving propranolol had slower heart rate, shortness of breath, and fatigue.

TABLE I Comparison of First Occurrences of Orthostatic Hypotension and Hypotension

		Orthostatic Hypotension No. (%)		Hypotension No. (%)	
Therapy	No. of Pts	First Occurrences	No. of Events	First Occurrences	No. of Events
Quinapril	1,771	222 (12.5)	324	32 (1.8)	65
Placebo	338	46 (13.6)	72	0	0
Enalapril	339	32 (9.4)	38	5 (1.5)	6
Captopril	186	16 (8.6)	20	4 (2.2)	7

Reproduced with permission from Frank et al.[24]

Similar results have been reported in comparative studies of newer ACE inhibitors with other drug classes. In clinical trials of enalapril in moderate hypertension,[51] the greatest increase in adverse reactions after 16 weeks of therapy occurred in patients treated with atenolol, the next greatest was seen in those receiving hydrochlorothiazide, and the smallest increase was recorded in those receiving enalapril. Intergroup differences were statistically significant ($p < 0.05$).

In clinical trials of lisinopril for hypertension, the ACE inhibitor was compared with a calcium antagonist and β blocker. Clinical side effects (none serious) developed in 21% of 89 patients randomized to lisinopril and 49% of 47 patients randomized to nifedipine ($p \leq 0.01$) in a 12-week, double-blind, multicenter trial.[52] Significantly ($p \leq 0.01$) more patients developed peripheral edema, flushing, and headache while receiving nifedipine than while receiving lisinopril. The most common lisinopril side effects were dizziness and diarrhea, reported by <5% of patients (not significantly different from nifedipine-treated patients).

COMPARATIVE STUDIES

In controlled clinical trials, quinapril has been compared with enalapril for the treatment of mild to moderate hypertension[53] and with captopril for moderate to severe hypertension.[54] Adverse effects are summarized in Tables II and III, respectively. The results of the comparison with enalapril showed fewer adverse events in the quinapril cohort; 7 patients withdrew because of side effects from quinapril compared with 10 patients in the enalapril group.[53] Fewer side effects with quinapril were reported in the comparative trial with captopril; no patient receiving quinapril experienced syncope.[54] Urticaria and nausea/vomiting necessitated withdrawal from cap-

TABLE II Patients (%) Reporting Adverse Events with a Rate >1%*

Adverse Events	Quinapril (n = 127)	Enalapril (n = 131)	Ramipril (n = 129)	Cilazapril (n = 3,769)
Headache	4.7	4.6	1.6	4.5
Coughing	3.1	6.1	—	1.6
Dizziness	2.4	5.3	3.1	3.3
Nausea/vomiting	—	5.3	3.9	—
Myalgia	1.6	3.1	—	—
Somnolence	2.4	2.3	—	—
Fatigue	—	3.8	—	1.7
Bronchitis	2.4	1.5	—	—
Rhinitis	2.4	—	—	—
Palpitation	—	3.1	—	—
Chest pain	—	2.3	—	—

* Compiled data.

TABLE III Most Frequently Reported Adverse Events During a Double-Blind Study

Adverse Events	Quinapril (n = 88) No. (%)	Captopril (n = 84) No. (%)
Dizziness	6 (7)	4 (5)
Back pain	1 (1)	4 (5)
Syncope	0	3 (4)
Headache	2 (2)	3 (4)
Diarrhea	2 (2)	3 (4)
Nausea/vomiting	5 (6)	3 (4)
Myalgia	4 (5)	3 (4)
Asthenia	0	3 (4)
Coughing	4 (5)	3 (4)
Pruritus	0	3 (4)
Chest pain	4 (5)	2 (2)
Fatigue	3 (3)	2 (2)
Dyspepsia	3 (3)	1 (1)

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topril therapy in 2 patients, whereas none in the quinapril group had to discontinue therapy because of side effects.

CONCLUSION

The elevation of ACE inhibitors to the category of first-line pharmacologic therapy for hypertension is based on accumulated experience demonstrating that these agents, when used properly, are associated with a relatively low incidence of clinical side effects and laboratory abnormalities. Adverse reactions to this drug class are usually not serious unless doses are excessive or there is underlying renal impairment or collagen vascular disease.

Safety and high patient tolerability of the newest entity, quinapril, have been reported in controlled clinical trials in which other ACE inhibitors as well as placebo and other classes of antihypertensive agents were used as comparative agents.

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Angiotensin-Converting Enzyme Inhibitors for Systemic Hypertension in Young and Elderly Patients

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Whereas many physicians have been reluctant to treat hypertension in the elderly because of perceived limited benefits and the risk of side effects associated with traditional antihypertensive agents such as diuretics and β blockers, studies and clinical experience have shown that elderly as well as younger patients can benefit from treatment. In recent years, angiotensin-converting enzyme (ACE) inhibitors have been found to be safe and effective in both young and elderly hypertensive patients without many of the adverse effects associated with traditional agents. ACE inhibitors possess characteristics that meet many of the special needs of elderly patients, including reduction of left ventricular mass, lack of metabolic and lipid disturbances, no central nervous system effects, no risk of induction of cardiac failure, and low risk of orthostatic hypotension.

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It is estimated that >50% of Americans aged >65 have essential hypertension. As the population ages, it is expected that in the near future the number of elderly hypertensive patients will reach at least 25 million.[1] As in the case of younger patients, elderly hypertensive patients will be at increased risk for congestive heart failure, stroke, cardiovascular disease, and other sequelae if their hypertension, including isolated systolic hypertension, is not treated adequately.[1-3]

Although the risks of hypertension have been well documented, it is estimated that <15% of the elderly receive adequate treatment.[1] The reluctance of clinicians to treat elderly hypertensive patients is due in part to persisting misconceptions about the pathophysiology of hypertension in this age group. In addition, treatment has been thought to provide marginal benefit while exposing the patient to the risk of potentially serious side effects associated with diuretics and β blockers, the more commonly used antihypertensive drugs. In recent years, calcium antagonists and angiotensin-converting enzyme (ACE) inhibitors have been increasingly used in the treatment of both young and elderly patients. This report reviews how the unique characteristics of ACE inhibitors can meet the needs of elderly patients.

PATHOPHYSIOLOGY OF HYPERTENSION IN THE ELDERLY

Hypertension poses essentially the same risks in both younger and older patients. However, there are various pathogenic factors that must be taken into account when devising a therapeutic strategy for the elderly patient with high blood pressure. Weber et al,[4] for example, maintain that hypertension in the elderly differs clinically and mechanistically from hypertension in the young. A complicating factor is that the effects of both age and long-standing hypertension on target structures are involved in the pathogenesis of hypertension in the elderly (Table I).[1]

Weber et al[4] proposed 3 mechanisms as the most dominant in sustaining systolic hypertension in the elderly: (1) tendency to sodium expansion; (2) enhanced sympathetic nervous system responsiveness; and (3) decrease in compliance of large arteries. About 33% of elderly patients with hypertension exhibit heightened aldosterone response to angiotensin II. Whereas plasma renin activity is relatively insensitive to changes in sodium bal-

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ance in these patients, the sensitivity of aldosterone to relatively small changes in angiotensin II appears to be increased.[4]

BENEFITS OF TREATING ELDERLY HYPERTENSIVE PATIENTS

Most of the large multicenter studies on the treatment of hypertension, such as the Hypertension Detection, and Follow-up Program[5] and the Australian study,[6] included patients over age 60. Whereas these studies indicated that patients in all age groups achieved reductions in blood pressure, they did not provide specific data on the reduction of cardiovascular risk in the elderly. Overall, these studies tended to show that treating hypertension resulted in a lowered incidence of mortality from stroke, but provided no clear evidence of a reduced incidence of coronary artery disease. The Systolic Hypertension in the Elderly Program[7] demonstrated that treatment with the diuretic chlorthalidone lowered systolic blood pressure. The European Working Party on High Blood Pressure in the Elderly trial[8] was 1 of the first studies designed to determine whether treatment of hypertension in patients over 60 years of age would result in reduced cardiovascular mortality and morbidity. In the double-blind phase of the trial, a significant reduction of 38% was seen in cardiovascular mortality, due largely to a 47% reduction in cardiac deaths. Deaths from myocardial infarction and cerebrovascular events were reduced by 60 and 43%, respectively. During this phase of the trial, there were 14 fewer cardiovascular deaths and 29 fewer cardiovascular events/1,000 patient years in the actively treated group.

TRADITIONAL ANTIHYPERTENSIVE AGENTS

The antihypertensive agents used in most of the large trials were those available at the time—diuretics, β blockers, and sympatholytic agents. Whereas these trials demonstrated the general efficacy of these agents, they also pointed out some of the problems associated with them for both elderly and younger patients.

Diuretics: Diuretics have been the traditional agent for initial therapy in elderly hypertensive patients. However, studies and clinical experience have shown that effective antihypertensive therapy with diuretics is often limited by side effects such as metabolic alterations and a negative impact on the quality of life.[9,10] Diuretic-induced hypokalemia has the potential for serious complications such as cardiac arrhythmias during long-term therapy, and elderly patients receiving digitalis are at particularly high risk for ventricular arrhythmias and sudden death from hypokalemia.[10] Diuretics have also been shown to increase serum cholesterol and serum triglyceride levels without increasing serum levels of the cardioprotective high-density lipoprotein cholesterol.[10] Common reactions leading to discontinuation of diuretics include gastrointestinal disturbances, sexual dysfunction, dizziness, lethargy, and weakness.[10]

TABLE I Effects of Age and Hypertension

Cardiovascular
Arterial stiffening: contributes to the development of isolated systolic hypertension with or without atherosclerosis.
Left ventricular hypertrophy: develops more quickly in a hypertensive patient in response to increases in cardiac afterload in an attempt to return elevated wall stress to normal. Left ventricular hypertrophy imposes as much as a five- to sixfold increase in risk for sudden death.
Baroreceptor reactivity: declines with age.
Renal and endocrine
Glomerular filtration rate: declines with age.
Creatinine clearance: declines with age, but creatinine also declines.
Renal blood flow: slowed, leading to reduced glomerular filtration rate.
Renin-angiotensin system: plasma renin and aldosterone activity decline.
β adrenoreceptors: reactivity declines.

Beta blockers: Beta blockers are generally recommended as initial therapy for younger patients but not elderly patients, since β-receptor sensitivity and renin activity are reduced in the elderly, contributing to the reduced efficacy observed with β blockers in older patients. In addition to numerous subjective side effects, decreased high-density lipoprotein cholesterol levels and glucose intolerance have been observed during long-term therapy with β blockers.[10]

Sympatholytics: Sympatholytic agents have not been associated with metabolic abnormalities, but they are poorly tolerated by many patients, particularly the elderly, mainly because of side effects related to their action on the central nervous system. Common side effects include orthostatic hypotension, lethargy, depression, and impotence. In the Hypertension Detection, and Follow-up Program, 27% of patients were withdrawn from therapy because of adverse experiences related to treatment with methyldopa.[10]

CALCIUM ANTAGONISTS

Calcium antagonists exert their antihypertensive action through a direct effect on smooth muscle tone and can provide effective control of blood pressure both as monotherapy and combined with a diuretic.[10] These drugs have been shown to be effective in elderly patients, but their usefulness in this application may be limited by their potent vasodilatory effects. Calcium antagonists may also impair insulin secretion and exacerbate glucose intolerance during short-term administration in nondiabetic patients.[10]

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

ACE inhibitors are a relatively new class of orally active cardiovascular agents that have been shown to be

effective in the treatment of hypertension and congestive heart failure without many of the side effects often associated with other antihypertensive drugs.[11] In contrast to diuretics, ACE inhibitors are not associated with metabolic or lipid abnormalities. In addition, ACE inhibitors do not act on the central nervous system or induce cardiac failure. Of significance to the elderly, postural orthostatic hypotension in the absence of volume depletion is not a risk associated with these agents.[12] ACE inhibitors can be safely administered with diuretics for additional blood pressure-lowering effects.[10]

Seven ACE inhibitors are available in the United States: benazeprilat, captopril, enalapril, fosinoprilat, lisinopril, quinapril, and ramipril, with several more under investigation. Captopril, the first ACE inhibitor to be introduced, differs from the others by the presence of a sulfhydryl group in its chemical structure.[13] This moiety is believed to be the cause of some of the adverse effects reported with captopril, including rash, pruritus, and taste disturbances, all of which occur more frequently with captopril than with the other agents. The nonsulfhydryl ACE inhibitors such as enalapril and quinapril have been shown to be effective when administered once daily, thus providing 24-hour blood pressure control (Figure 1).[14] In contrast, captopril must be administered 2–3 times daily.[15]

ACE inhibitors do not depress or impair cardiac or sexual function and do not adversely affect the central nervous system. In addition, normal autonomic and cardiovascular reflex functions are not affected, thereby preventing the reflex tachycardia that occurs with some antihypertensive drugs.[10] ACE inhibitors, moreover, are a particularly appropriate choice for patients with left ventricular hypertrophy since they decrease left ventricular mass.[4]

Pharmacokinetics: Generally, ACE inhibitors are rapidly absorbed, and peak serum levels are reached in 1–2 hours. Quinapril, for example, reaches peak plasma concentration within 1 hour and has an apparent half-life of 50 minutes. After absorption, quinapril is converted to its active metabolite, quinaprilat, which is a considerably more potent ACE inhibitor than its parent compound.[14]

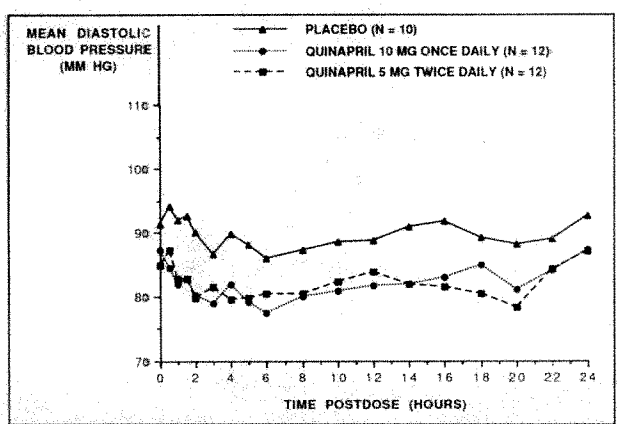


FIGURE 1. Mean 24-hour diastolic blood pressure at steady state after quinapril administration, 10 mg once daily or 5 mg twice daily.

Studies have been conducted to determine the pharmacokinetics of quinapril and quinaprilat in elderly and young patients.[14] Mean creatinine clearance was 99 and 62 mL/min in young and elderly patients, respectively. The rate of hydrolysis of quinapril to quinaprilat and the rate of elimination of quinaprilat were slower in elderly patients than in young patients. The somewhat decreased rate of elimination in elderly patients, however, was due to changes in renal function related to aging and not to age itself. Thus, the rate of quinaprilat elimination in the elderly can be determined from the expected age-related reductions in renal function.[14] Olson et al[16] demonstrated a 96% recovery rate of quinaprilat from urine within 24 hours of drug administration. These data suggest that accumulation of the metabolite in plasma with repeated dosing of quinapril is unlikely.

Hockings et al[17] compared the pharmacokinetics of enalapril and enalaprilat in elderly and young volunteers. The area under the plasma concentration–time curve was greater for both compounds in the elderly patients. A significant difference in the weight-corrected volume of distribution at steady state between the young and elderly patients after enalaprilat ($p < 0.02$) was also observed. There was no difference in the sensitivity to ACE inhibition between the 2 groups. Gautam et al[18] found that elderly patients had higher serum concentrations of lisinopril after receiving lisinopril 5 mg daily for 7 days than did younger subjects receiving the same dosage.

In a study of captopril in healthy elderly volunteers,[19] Creasey et al found that the maximum plasma concentration and area under the curve were 9 and 13% greater, respectively, than those observed in a previously tested group of young volunteers. However, 24-hour urinary excretion and 8-hour renal clearance were 25 and 36% lower, respectively, in the older volunteers.

ACE inhibitors are less likely to interact with other drugs used frequently by elderly patients. Ferry et al[20] found that concomitant multiple-dose administration of quinapril did not alter the steady-state pharmacokinetics of digoxin. Quinapril also does not influence the pharmacokinetics of cimetidine or warfarin.[14]

Mechanism of action: The primary mechanism of action of ACE inhibitors is believed to be suppression of the renin–angiotensin–aldosterone system. Renin, produced by the kidneys, acts on a plasma globulin substrate to yield angiotensin I, a relatively inactive decapeptide. Angiotensin I is converted to angiotensin II, a potent vasoconstrictor and the primary stimulus for the production of aldosterone by ACE. ACE inhibitors bind stoichiometrically with the active site of ACE, thereby inhibiting its action.[21] Other possible mechanisms include:[22]

attenuation of catecholamine response from noradrenergic nerve endings; blunting of the arterial baroreceptor reflex; and increasing bradykinin–prostaglandin tissue levels.

The renin–angiotensin system has been thought to be mainly an endocrine system with the activity of angiotensin II confined to the circulation only.[22] ACE, however, has been found in a number of tissues, including blood vessels, brain, endothelium, kidney, adrenals, lung, and the gastrointestinal and reproductive tracts.[21] Specific angiotensin binding sites have been found in the aorta and in large, medium, and small arteries.[22] It is now apparent that the long-term antihypertensive effect of ACE inhibitors is probably dependent on inhibition of tissue ACE and that its acute antihypertensive effects are induced by decreases in circulating angiotensin II.[21] If the degree and duration of the antihypertensive action of ACE inhibitors are determined by tissue rather than serum concentration, the serum half-life of an ACE inhibitor probably has little to do with its long-term blood pressure-lowering effects.[22]

Reduction of tissue ACE activity by ACE inhibitors has been demonstrated in animal and human studies. Inhibition of both plasma and aortic ACE was shown in rats administered oral quinapril.[23] Aortic ACE inhibition correlated well with blood pressure reduction whereas that of plasma did not. In a study of 15 elderly hypertensive patients, 20–40-mg doses of quinapril were administered once daily for 28 days.[24] Peak mean diastolic blood pressure reductions of 13.9 and 17.3 mm Hg were seen at 3 and 2 hours after the dose on days 1 and 28, respectively. When the plasma concentrations of quinapril and its active metabolite were compared with blood pressure reductions at individual time points, no correlation was found. Accordingly, a much better relation is apparent between the blood pressure-lowering effect of quinapril and aortic ACE inhibition, suggesting that vascular tissue ACE inhibition may be more important than plasma ACE inhibition in the antihypertensive effect and overall clinical profile of this drug.

It has also been shown that 24 hours after withdrawal of long-term therapy with an ACE inhibitor, serum ACE activity returned to pretreatment levels.[22] However, tissue ACE activity and blood pressure remained reduced. The duration of antihypertensive response paralleled the suppression of ACE activity in the aorta and kidney but not in serum, an indication that ACE inhibitors exert their action primarily through inhibition of ACE in local tissue. These data suggest that a local renin–angiotensin system exists in blood vessel walls and contributes to the maintenance of vascular tone.[22]

Role of renin activity: When ACE inhibitors were first introduced, it was thought they would not be particularly useful in elderly hypertensive patients because of the decreasing renin activity that accompanies aging.[25] Recent data, however, suggest that, consistent with their effects at the local tissue level, ACE inhibitors are effective in hypertensive patients with low, medium, and high plasma renin activity.[22] Furthermore, plasma renin activity tends to be low in both normotensive and hypertensive elderly patients. It is therefore unlikely that a direct vasoconstrictor effect of the renin–angiotensin system is involved in maintaining blood pressure.[4] Whereas plasma renin activity in low-renin hypertensive patients appears to be relatively insensitive to changes in sodium balance, the sensitivity of aldosterone to small changes in angiotensin II is increased in this type of hypertension.[4]

Efficacy and tolerability: The efficacy and safety of quinapril in the treatment of mild, moderate, and severe hypertension were assessed in a series of controlled clinical studies in which 2,499 patients participated.[14] In placebo-controlled trials, quinapril was found to be effective at dosages of 10–80 mg/day.

Analyses of safety data indicated comparable safety profiles for quinapril, enalapril, and placebo. However, the safety profiles of these 2 agents and placebo were more favorable than those of captopril and chlorthalidone. Patients receiving quinapril had a lower incidence of orthostatic events than did those treated with captopril, enalapril, or placebo, and the incidence of first-dose hypotensive effects, which can be particularly hazardous in elderly patients, was comparable to that of placebo. In a subset analysis of 451 elderly patients (≥65 years of age) the type and frequency of adverse events were found to be similar for both elderly and younger adult hypertensive patients treated with quinapril.[14]

In a separate study, elderly hypertensive patients (≥65 years) were randomized to receive either captopril 50 mg twice daily or chlorthalidone 25 mg once daily for 3 months. Significant decreases in blood pressure were seen in both groups. Although metabolic changes occurred in both groups, significant increases in plasma glucose and triglycerides and decreases in serum potassium were observed in patients receiving chlorthalidone.[10]

Grosskopf et al[12] compared the safety and efficacy of enalapril (10–40 mg daily) to hydrochlorothiazide (25–100 mg daily) in the treatment of hypertension in 32 patients aged 63–82 years. Most patients in both groups achieved goal blood pressure. However, 4 patients in the enalapril group and 3 in the hydrochlorothiazide group withdrew from the study because of side effects. Adverse effects causing withdrawal were postural hypotension, dizziness, nausea, and weakness in the enalapril group and postural hypotension, rash, and fatigue in the diuretic treatment group.

In a study of 172 patients with moderate to severe hypertension, the efficacy and safety of quinapril (20–80 mg daily) was compared to captopril (50–200 mg daily).[26] After a minimum of 4 weeks of therapy, significantly greater reductions in blood pressure ($p < 0.05$)

were achieved in the quinapril group (18.6 mm Hg) than in the captopril group (15.0 mm Hg). Hypotensive events (decreases >20 mm Hg) occurred in 4 patients in the quinapril group (4 total episodes) and in 7 patients receiving captopril (8 total episodes). Five patients receiving captopril were withdrawn from the study because of side effects, whereas no patients in the quinapril group were withdrawn.

CONCLUSION

ACE inhibitors have been shown to be equally efficacious and well tolerated in both elderly and young patients. In addition, these agents have the potential to meet the needs of elderly patients without many of the adverse effects that have limited the use of diuretics, β blockers, and sympatholytics in this population. ACE inhibitors do not induce potassium loss and have no adverse effects on lipid metabolism.

ACE inhibitors not containing a sulfhydryl group (enalapril, lisinopril and quinapril) are generally more effective and are associated with fewer adverse effects than captopril. Other favorable characteristics of ACE inhibitors include inhibition of ACE in both tissue and plasma, lack of interaction with drugs used frequently by elderly patients, and lack of accumulation in plasma. Compliance, which is often difficult in older patients, can be enhanced by the once-a-day regimens and 24-hour control possible with ACE inhibitors such as quinapril.

It is now generally accepted that hypertension is a major risk factor for elderly as well as younger patients and should be treated adequately in both groups. In the past, many elderly hypertensive patients were not treated because of side effects and the negative impact on quality of life associated with commonly used agents. With the advent of effective, better tolerated agents such as ACE inhibitors, it is likely that more elderly hypertensive patients will receive the treatment they need.

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Angiotensin-Converting Enzyme in Renal and Cerebral Tissue and Implications for Successful Blood Pressure Management

Garry P. Reams, MD

In addition to the classic circulating renin–angiotensin system, increasing evidence supports the existence of local tissue renin–angiotensin systems (vascular, cardiac, kidney, and brain) that appear to participate in cardiovascular homeostasis and in the pathogenesis of cardiovascular disorders via multiple autocrine and paracrine functions. Components of local systems have been detected in cardiovascular tissues. Studies with angiotensin-converting enzyme (ACE) inhibitors provide further evidence of the existence and importance of tissue renin–angiotensin systems. The blood pressure-lowering effect of quinapril, for example, correlated better with inhibition of tissue ACE (aorta) than with inhibition of plasma ACE. The effects of ACE inhibitors on local tissue renin–angiotensin systems (vascular in particular) may be the crucial determinant of response to treatment. Newer ACE inhibitors, such as quinapril, have favorable side effect profiles as well as apparent tissue specificity for the vascular renin–angiotensin system (and possibly other relevant cardiovascular tissue). Differentiation among ACE inhibitors should play an even more important role in the future for individualization of therapy.

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The classic circulating renin–angiotensin system consists of the enzyme renin, which acts on its substrate to form angiotensin I, a physiologically inactive decapeptide that is converted to the octapeptide angiotensin II by angiotensin-converting enzyme (ACE). This enzyme is found in all endothelia in the vascular system as well as in serum. In addition, components of the renin–angiotensin system have been found in such tissues as blood vessel walls, kidney, brain, heart, and adrenal gland.[1]

KIDNEY RENIN–ANGIOTENSIN SYSTEM

Although the kidney is the predominant source of circulating renin, it is also an apparent site for a tissue renin–angiotensin system, with angiotensin II acting as a renal vascular hormone. Immunologic techniques have localized components of the renin–angiotensin system in the renal cortex. Renin has been found in afferent and efferent arterioles, interlobular arteries, and in proximal and cortical collecting tubules. Angiotensin I and II appear to be present in juxtaglomerular cells and angiotensin receptors have been found in glomeruli and cortical tubular fractions.[1] ACE immunoreactivity has been observed in proximal tubules. The total amount of renal ACE is lower than in the lung, but renal ACE activity is localized to the juxtaglomerular apparatus, the site of renin release.[2]

Molecular genetic studies have demonstrated renin and angiotensinogen messenger RNA (mRNA) in the kidney, with renin mRNA localized primarily to the juxtaglomerular cells and angiotensinogen mRNA in the proximal tubules. However, immunoreactive renin but not renin mRNA has been detected in the proximal tubule.[3] These studies further suggest the complexity and diversity of local renin–angiotensin systems. Local tissue-specific regulation of angiotensin, responsive to different factors, appears to exist. In the rat, renal angiotensinogen mRNA was affected by dietary sodium and increased at puberty, whereas hepatic angiotensinogen mRNA was not affected by sodium and remained relatively constant during development.[4]

Renal renin–angiotensin may affect renal blood flow, glomerular filtration rate, glomerular hemodynamics, and sodium reabsorption. This intrarenal system probably plays an important role in sodium transport. Angiotensin is known to be a potent stimulator of sodium

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resorption and hydrogen ion secretion in the proximal tubule. Moreover, the intrarenal renin–angiotensin system itself appears to be regulated by sodium. Increased renin and angiotensinogen mRNA levels were seen in the kidney with a low-sodium diet.[3] Impairment of renal perfusion by disease (e.g., bilateral renal artery stenosis or congestive heart failure) results in activation of the renal renin–angiotensin system and stimulation of prostaglandin synthesis with preservation of glomerular filtration rate.[5]

Angiotensin II and prostaglandins exert opposite effects in the modulation of renal function via their actions on renal blood flow and salt and water balance. In normal subjects with a normal sodium diet, the renin–angiotensin system and renal prostaglandins seem to have little effect on renal perfusion and function.[5] In low perfusion states such as congestive heart failure, activation of the renal renin–angiotensin system and prostaglandin synthesis can produce vasoconstriction (predominantly of the efferent arteriole) and vasodilation (of the afferent arteriole), respectively. Glomerular capillary hydraulic pressure and filtration fraction are increased and glomerular filtration rate is preserved.

BRAIN RENIN–ANGIOTENSIN SYSTEM

Similar studies have demonstrated the presence of renin–angiotensin components in the brain tissue of nephrectomized dogs.[6] Widespread distribution of ACE (as well as renin mRNA) in the brain has been shown, generally with a close correlation with the distribution of angiotensin II in different areas. Specific angiotensin II receptors have been localized to particular brain areas, with good correlation with angiotensin II immunoreactivity (although some dissociation has been noted) in other areas.[7] The expression of angiotensinogen and renin genes in the brain has been demonstrated,[5] corroborating earlier biochemical studies that suggested the existence of a brain renin–angiotensin system.

A tissue-specific regulation of brain angiotensinogen has been suggested by the observed dissociation between the brain and hepatic responses of angiotensinogen mRNA to adrenalectomy, nephrectomy, and dexamethasone administration.[7]

Extensive studies with ACE inhibitors have suggested that tissue renin–angiotensin systems play an important role in cardiovascular homeostasis. Reductions in ACE activity in the brain have been demonstrated after intracerebroventricular and systemic administration of a variety of ACE inhibitors to animals. Dissociation of central blockade from blockade of peripheral circulating ACE has also been shown.[6]

Brain angiotensin may affect regulation of blood pressure, thirst, vasopressin and catecholamine release, and behavior.[1] Differences have been noted between the effects of brain and circulating angiotensin II. Intracerebroventricular injection of angiotensin II at doses well below the pressor threshold induced sustained natriuresis, whereas circulating angiotensin II resulted in sodium retention. Moreover, some of the effects of circulating angiotensin II may be exerted via stimulation of brain angiotensin receptors.[7]

Biochemical, neurophysiologic, pharmacologic, and molecular genetic studies have provided evidence that the brain renin–angiotensin system is regulated differentially and independently of the circulating renin–angiotensin system. For example, after long-term salt loading in spontaneously hypertensive rats, brain ACE activity increased but aortic ACE decreased. Angiotensin-containing pathways within brain areas involved in central blood pressure regulation have also been identified.[7] Use of ACE inhibitors has supported the concept of a role for the central brain renin–angiotensin system. For example, administration of an ACE inhibitor into the central nervous system resulted in lowered blood pressure and inhibition of thirst.[1]

Two angiotensin II-sensitive areas identified in the brain, the subfornical organ and the organum vasculosum of the lamina terminalis, lack a blood–brain barrier due to their fenestrated vasculature. This lack of a blood–brain barrier permits them to react to both blood-borne and brain angiotensin. Intravenous angiotensin II produced induction of drinking, increased blood pressure, and release of hypophyseal hormones, whereas angiotensin II from the cerebrospinal fluid did not readily activate the subfornical organ. However, direct angiotensin II-containing projections have been found that connect the subfornical organ with other brain areas, suggesting that the effects of brain angiotensin may be transmitted via neuronal pathways without stimulation by cerebrospinal fluid-borne angiotensin II.[7]

By contrast, the organum vasculosum of the lamina terminalis was affected by both cerebrospinal fluid and blood angiotensin and this area may be an important site for cerebrospinal fluid-borne angiotensin II. Lesions involving the organum vasculosum of the lamina terminalis resulted in blocked response to both intravenous and intracerebroventricular angiotensin II, as well as hypernatremia and adipsia. However, it is not known whether the effects were due to direct destruction of receptor areas or disruption of efferent projections from the subfornical organ to these areas.[7]

EFFECTS OF CIRCULATING VERSUS LOCAL RENIN–ANGIOTENSIN SYSTEMS

Two methods of radio-inhibitor binding to tissue membrane homogenates and in vitro autoradiography (allowing localization of ACE inhibition to very discrete anatomical areas) were used in ex vivo studies of tissue

ACE inhibition after acute and chronic administration of ACE inhibitors. These studies demonstrated variable patterns of induction and inhibition of converting enzyme in different tissues.[8]

For example, tissue ACE was differentially inhibited in various tissues in rats. Low doses of ACE inhibitors resulted in complete ACE inhibition in plasma, kidney, and brain areas outside the blood–brain barrier; very high doses produced inhibition of only 60–70% of lung and aorta ACE and of 20–40% in the brain within the blood–brain barrier.[8]

On the basis of recent data, it has been postulated that short-term cardiovascular homeostasis is the responsibility of the circulating renin–angiotensin system, whereas the tonic control of cardiac, renal, and vascular function is influenced by the intrinsic tissue renin–angiotensin system (which adds little to levels of circulating renin–angiotensin).[1] During periods of cardiovascular decompensation, the circulating renin–angiotensin system is activated to provide acute homeostasis. During the chronic compensated "non-renin-dependent" phases of congestive heart failure and renovascular hypertension, when the acute support of the circulating renin–angiotensin system is no longer needed, the tissue renin–angiotensin systems may maintain vascular tone and cardiac function.[1]

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Tissue inhibition: Studies in animals and humans suggest that ACE inhibitors exert their primary effect at local tissue sites.[9] In 2-kidney, 1-clip Goldblatt hypertensive rats, there was a good correlation between the inhibition of vascular ACE and blood pressure lowering and a poor correlation between blood pressure lowering and plasma and brain ACE inhibition.[10]

In a study of elderly hypertensive patients who received the ACE inhibitor quinapril for 28 days, diastolic blood pressure was effectively reduced. Maximum plasma concentration of the drug and its active metabolite occurred within 2 hours after the dose, but there was no apparent correlation between plasma drug concentration and efficacy. This finding suggests that tissue drug concentration (and presumably, tissue effects) may be more important than plasma drug concentration.[11]

ACE inhibitors seem to remain bound to tissue ACE much longer than to plasma ACE, and the duration of action of ACE inhibitors may, therefore, be related more closely to tissue binding than to inhibition of plasma ACE. Persistence of ACE inhibition in local tissues was suggested by the observations that 24 hours after withdrawal of long-term ACE inhibitor therapy, when serum ACE activity and pressor response to exogenous angiotensin had returned to normal, blood pressure and tissue ACE activity remained suppressed. The duration of the antihypertensive effect paralleled the inhibition of renal and aortic ACE but not of serum activity, suggesting that ACE inhibitors exert their effect primarily by inhibiting local angiotensin II production.[9]

After oral administration of the ACE inhibitor quinapril to rats, there was a substantial reduction in plasma ACE, maximal at 1–2 hours, and about 25% at 24 hours. In the lung and aorta, ACE inhibition was less and lasted >24 hours. Plasma quinaprilat levels showed a converse pattern (Figure 1). Similar differential tissue effects were seen with the other ACE inhibitors studied, benazepril and perindopril.[8]

Differences among angiotensin-converting enzyme inhibitors: ACE inhibitors differ in tissue distribution and duration of action, and differences in drug me-

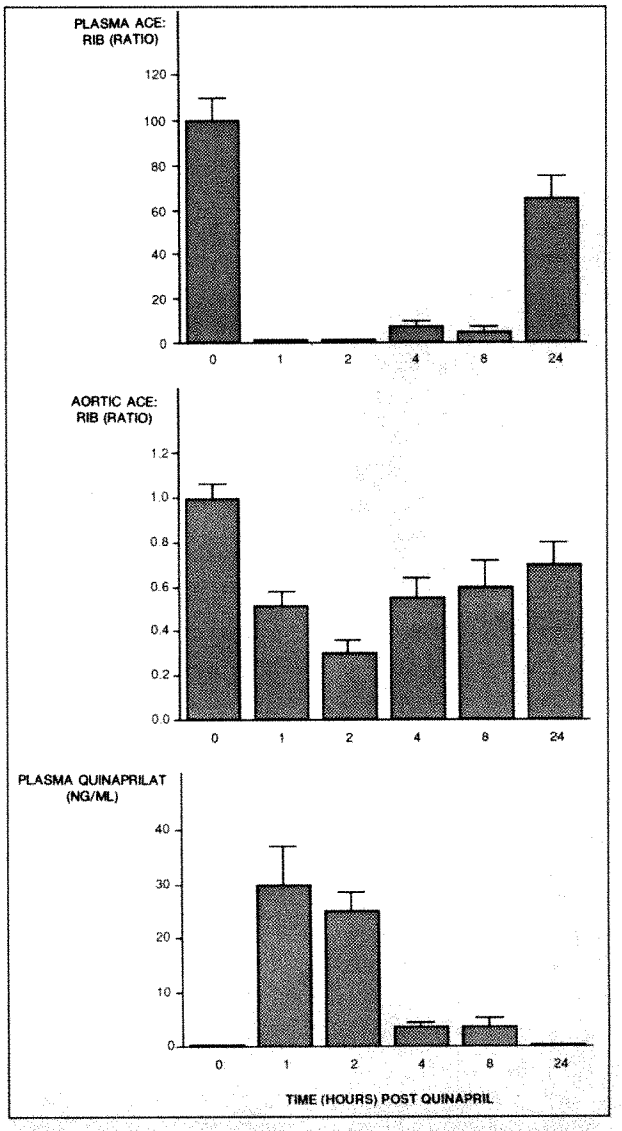


FIGURE 1. Time course of angiotensin-converting enzyme inhibition in plasma and aorta (by radio-inhibitor binding assay) and plasma concentration of quinaprilat after oral quinapril 0.3 mg/kg in rats. RIB = radioisotope binding. Reproduced with permission from *J Hypertens*.[8]

TABLE I Relative Potencies of Angiotensin-Converting Enzyme Inhibitors Determined by Radio-Inhibitor and Enzymatic Assays

Inhibitor	IC_{50} mmol/liter (Enzymatic)	ID_{50} mmol/liter (Radio-Inhibitor) Displacement	Potency
Captopril	0.22×10^{-7}	0.16×10^{-8}	Lowest
Perindoprilat	0.18×10^{-8}	0.25×10^{-8}	Moderate
Benazeprilat	0.13×10^{-8}	0.40×10^{-10}	Moderate
Quinaprilat	0.55×10^{-10}	0.45×10^{-10}	Highest

Reproduced with permission from *J Hypertens*.[8]
IC_{50} = molar concentration needed to produce 50% inhibition of enzymatic activity; ID_{50} = molar concentration needed to displace 50% of the radioligand bound to the enzyme.

tabolism can affect their activity. Differential effects have been noted also for interference with sympathetic responses, perhaps attributable to varying tissue penetration and distribution.[12]

Differences in the distribution of tissue ACE inhibition have been shown in a study of oral administration of enalapril or captopril in spontaneously hypertensive rats at equidepressor doses. Both drugs produced prolonged duration of ACE inhibition in the aorta. However, captopril produced a more rapid and marked inhibition of brain ACE whereas enalapril caused greater inhibition of renal ACE.[1]

The chemical structure and physicochemical properties of ACE inhibitors also may explain their differing effects. Significant differences in molecular weight and polarities, for example, can affect tissue distribution and elimination. Moreover, for ACE inhibitors that are prodrugs, the site and degree of metabolic activation can influence access to the central nervous system as well as to other tissues.[6]

Differences in central ACE inhibition after systemic administration have been observed, presumably related to differences in penetration across the blood–brain barrier related to lipid solubility. In 1 study, enalapril, perindopril, and ramipril all reduced ACE activity in the cortex but only ramipril affected other brain areas.[6]

Differences also exist among ACE inhibitors with respect to potency, as measured by radio-inhibitor binding and conventional enzymatic techniques. Studies with 4 inhibitors (quinapril, benazepril, perindopril, and captopril) and the 3 prodrug esters (quinaprilat, benazeprilat, and perindoprilat) have indicated that the ester prodrug compounds were several orders of magnitude less potent than the active diacid compounds. Quinaprilat was the most potent. The molar concentrations needed to displace 50% of the radioligand bound to the enzyme (ID_{50} values) were similar for rank order of relative potencies compared to the concentrations needed to produce 50% inhibition of enzymatic activity (IC_{50} values) (Table I).[8]

Thus, the experimental data indicate that ACE inhibitors exert their main action at local tissue sites. The effect on local renin–angiotensin systems can influence the activity of an individual drug. Additional effects at local sites may result from the unique structural properties of specific agents.

MANAGEMENT OF HYPERTENSION

ACE inhibitors are viewed as particularly useful in the treatment of hypertension. Hemodynamically, ACE inhibitors act as vasodilators. They produce reductions in total peripheral resistance, a primary mechanism in the pathogenesis of hypertension, generally without adverse effects on heart rate and cardiac output. ACE inhibitors also may have other beneficial effects on the renin–angiotensin systems.[13]

Initially, it was noted that the overall responsiveness of captopril (the first commercially available ACE inhibitor) was related to pretreatment plasma renin activity; patients with hyperreninemia responded best to treatment. The drug became a major choice for the treatment of renovascular hypertension in patients with unilateral occlusive lesions. Later observations showed that captopril was effective in a wide range of patients with essential hypertension, regardless of pretreatment plasma renin activity level. Inhibition of circulating angiotensin II production could not explain the action of ACE inhibitors in patients with normal or low plasma renin activity.[13] On the other hand, differential converting enzyme inhibition in these tissues with blockade of local angiotensin II at vascular, brain, kidney, heart, and other sites may account for the clinical findings in some of these patients.

Short- and long-term effects: The circulating and tissue renin–angiotensin systems appear to differ with respect to the short- and long-term effects of ACE inhibitors. The role of the renin–angiotensin system in blood pressure regulation in acute conditions associated with elevated plasma renin activity was predictable and confirmed by studies with acute use of ACE inhibitors. However, plasma renin activity is often normal during the chronic phases of these cardiovascular disorders even though responses to long-term ACE inhibition persist. In humans, for example, the immediate depressor response tends to correlate with initial plasma renin activity, whereas the long-term response appears generally unrelated to pretreatment plasma renin activity level.[1]

Although the major contribution of the circulating renin–angiotensin system is short-term response to ACE inhibitors, the principal mechanism of the long-term antihypertensive action of these agents is most likely inhibition of ACE in the blood vessels and possibly other tissues, such as heart and kidney. Therefore, the serum half-life of ACE inhibitors would be expected to have little relation to the actual duration of the pharmacologic

effect of these drugs during long-term therapy. Instead, the concentration of the ACE inhibitors in certain tissues (vascular, renal, cardiac) would determine the magnitude and duration of action of the drug.

Adverse effects: Metabolically, ACE inhibitors are relatively neutral compared to other antihypertensive drugs in their lack of adverse effects on cholesterol (an important cardiovascular risk factor), carbohydrate metabolism, and uric acid levels.[14] For example, available data suggest that the ACE inhibitors captopril, enalapril, and quinapril do not adversely affect atherogenic blood lipoprotein levels.[15]

An annoying cough, which disappears with discontinuation of therapy, and angioedema, a rare but potentially serious side effect, appear to be class effects. Additionally, some patients with critical bilateral renal arterial disease or unilateral disease with 1 kidney are at increased risk for acute renal failure, probably because of the lack of the autocrine/paracrine autoregulatory adaptive mechanisms within the kidney.[14]

Individualization of therapy: The current trend in the management of patients with hypertension is toward individualization of therapy, with treatment tailored to the needs of the particular patient. The characteristics of ACE inhibitors make them particularly suitable for use in certain types of patients, including those with essential hypertension. These agents also have proven efficacious in long-term therapy regardless of pretreatment plasma renin activity, consistent with their inhibition of both circulating and local renin–angiotensin systems.[14] In the subgroup of nonmodulators, ACE inhibitors have been shown to reverse renal vasoconstriction and restore the ability of the kidney to handle a sodium load, as well as control blood pressure.[2]

Studies with ACE inhibitors have shown that they reduced proteinuria in diabetic patients with nephrotic syndrome, as well as lowered blood pressure and improved renal function. Diuretics and β blockers may have adverse effects on these patients, and peripheral α-adrenergic receptor blockers and calcium antagonists have not been clearly shown to have specific efficacy in this subgroup of patients.[16]

Differences among angiotensin-converting enzyme inhibitors: Although numerous differences have been observed among ACE inhibitors, the relative clinical importance of these differences has not been established. No clinical study is available comparing the tissue effects of different converting enzyme inhibitors and relating these findings to relative efficacy and side effects.

Differences also may exist among ACE inhibitors with respect to side effects profiles. In comparative studies with captopril, enalapril, and quinapril, all 3 ACE inhibitors were generally well tolerated with similar types of side effects, but quinapril had the lowest incidence of adverse effects in double-blind studies.[17]

CONCLUSION

The concept of local tissue renin–angiotensin systems that play a role in cardiovascular homeostasis is supported by multiple lines of experimental and clinical evidence. These renin–angiotensin systems exhibit numerous and varied cardiovascular effects. Different roles may exist for circulating versus tissue renin–angiotensin systems. For example, the renal renin–angiotensin system may be particularly important in conditions of renal hypoperfusion and an overactive brain renin–angiotensin system may be related to the pathogenesis of hypertension. The circulating renin–angiotensin system may be predominantly responsible for acute homeostasis, while tissue renin–angiotensin systems may regulate long-term cardiovascular homeostasis.

Inhibitors of the renin–angiotensin system (such as ACE inhibitors) are useful for the study of tissue renin–angiotensin systems as well as for the individualized treatment of cardiovascular disorders. These agents act as vasodilators hemodynamically and have been shown to be efficacious in the treatment of hypertension and congestive heart failure with a very favorable tolerability profile. The advent of newer agents, particularly those with improved side effects profiles (e.g., quinapril), will allow for further individualization of therapy. Differences among these agents have permitted better understanding of circulating and tissue renin–angiotensin systems and may be related to differences in converting enzyme inhibition produced at the tissue level, which can have important implications for both the efficacy and tolerability of a particular drug.

Research efforts related to the study of tissue renin–angiotensin systems must still overcome major methodologic difficulties. Only very low concentrations of renin–angiotensin system components may exist in individual tissues and particularly in specific organ areas. The effects of the circulating renin–angiotensin system must be separated from those of local renin–angiotensin systems. Interactions occur with other neuroendocrine systems that may confuse the interpretation of findings. Opposing effects may be produced in the same organ or in different organs within the same organ system. Appropriate assays are currently lacking to readily measure tissue ACE inhibition in humans.

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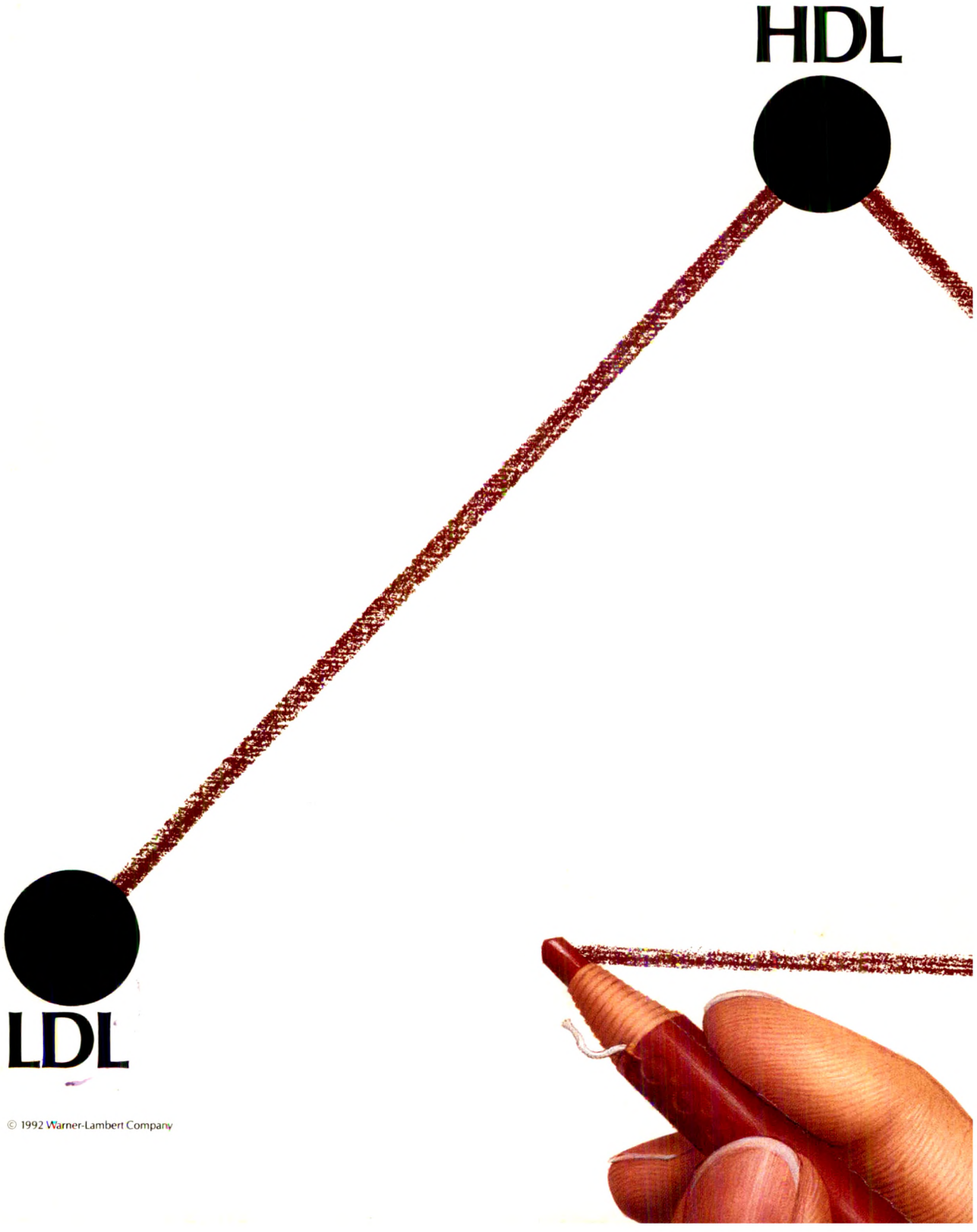
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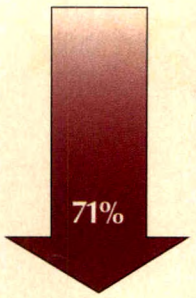
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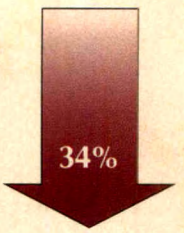
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Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

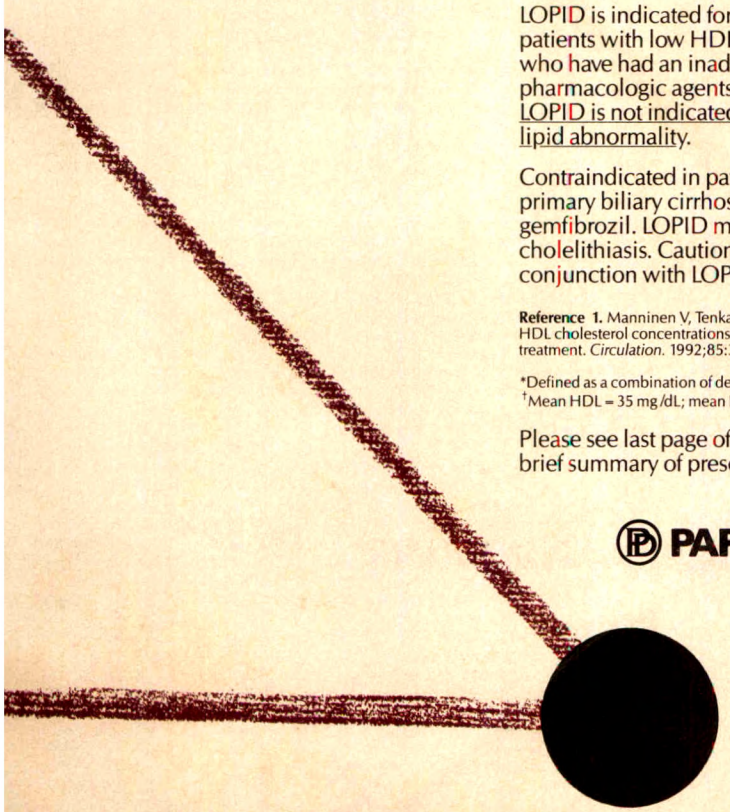
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*Defined as a combination of definite coronary death and/or definite myocardial infarction.
[†]Mean HDL = 35 mg/dL; mean LDL = 208 mg/dL; $P = .005$; 95% CI 21.2 to 118.6.

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A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

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2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

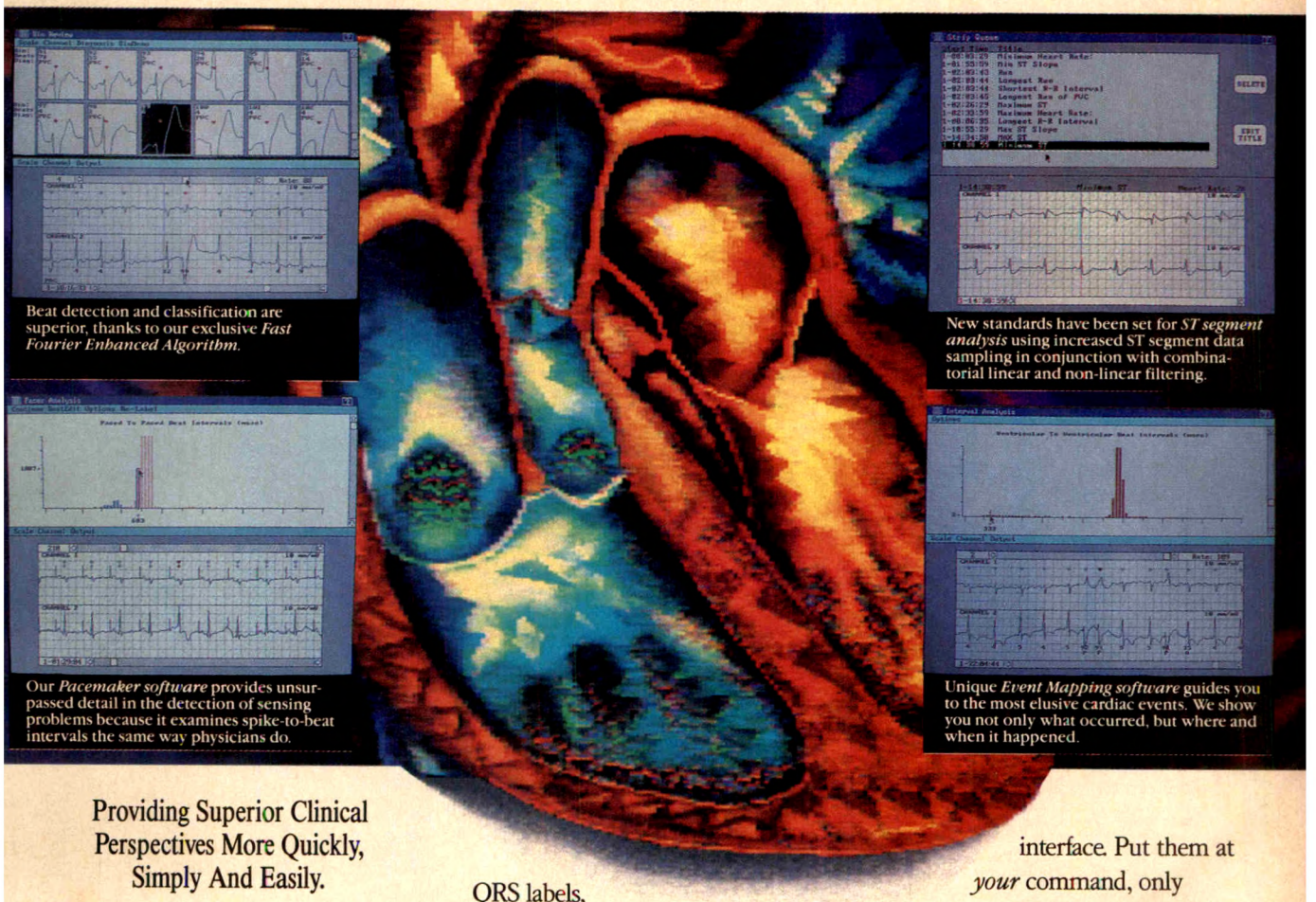
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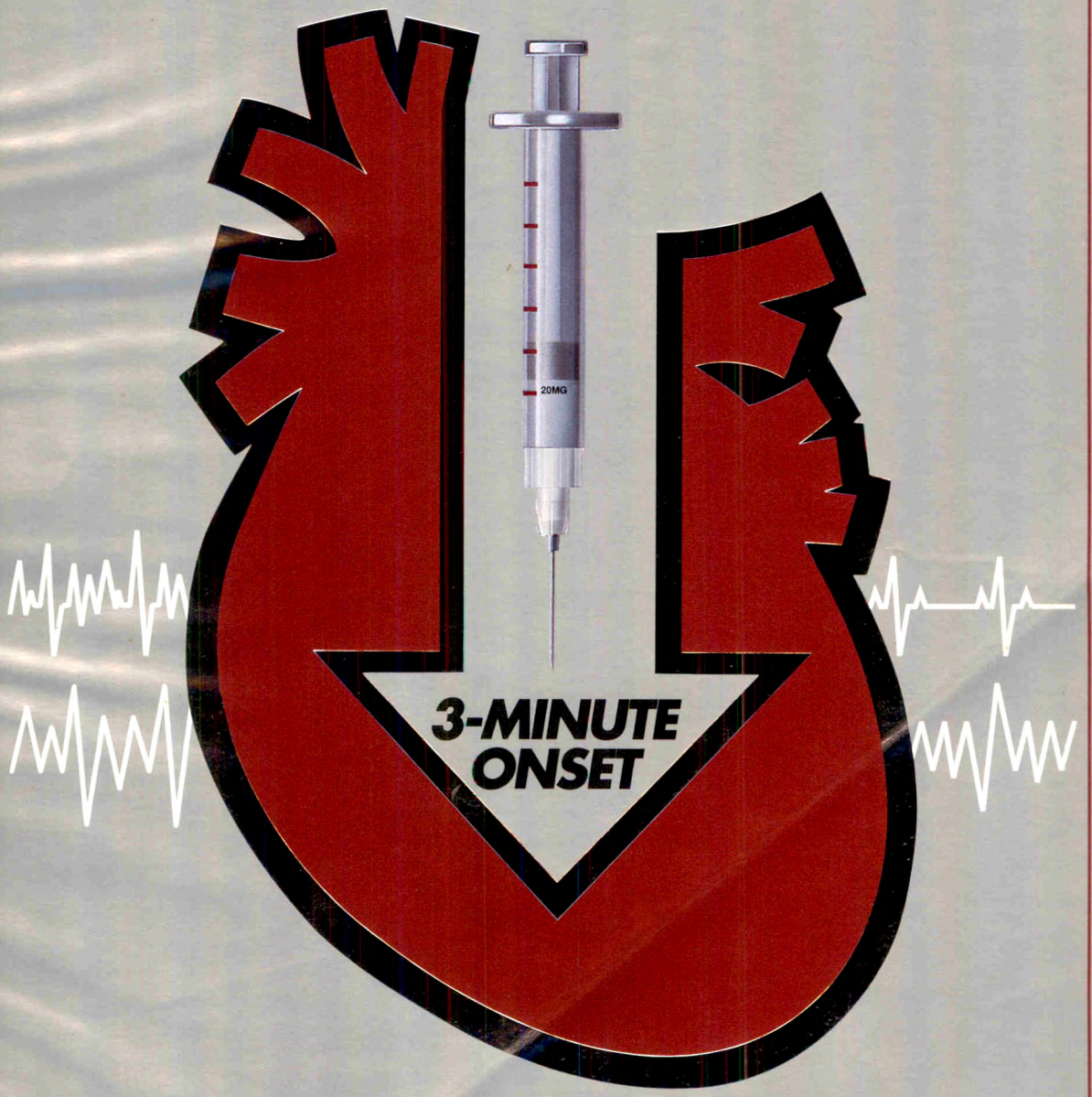
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GAINS HEART RATE CONTROL QUICKLY...

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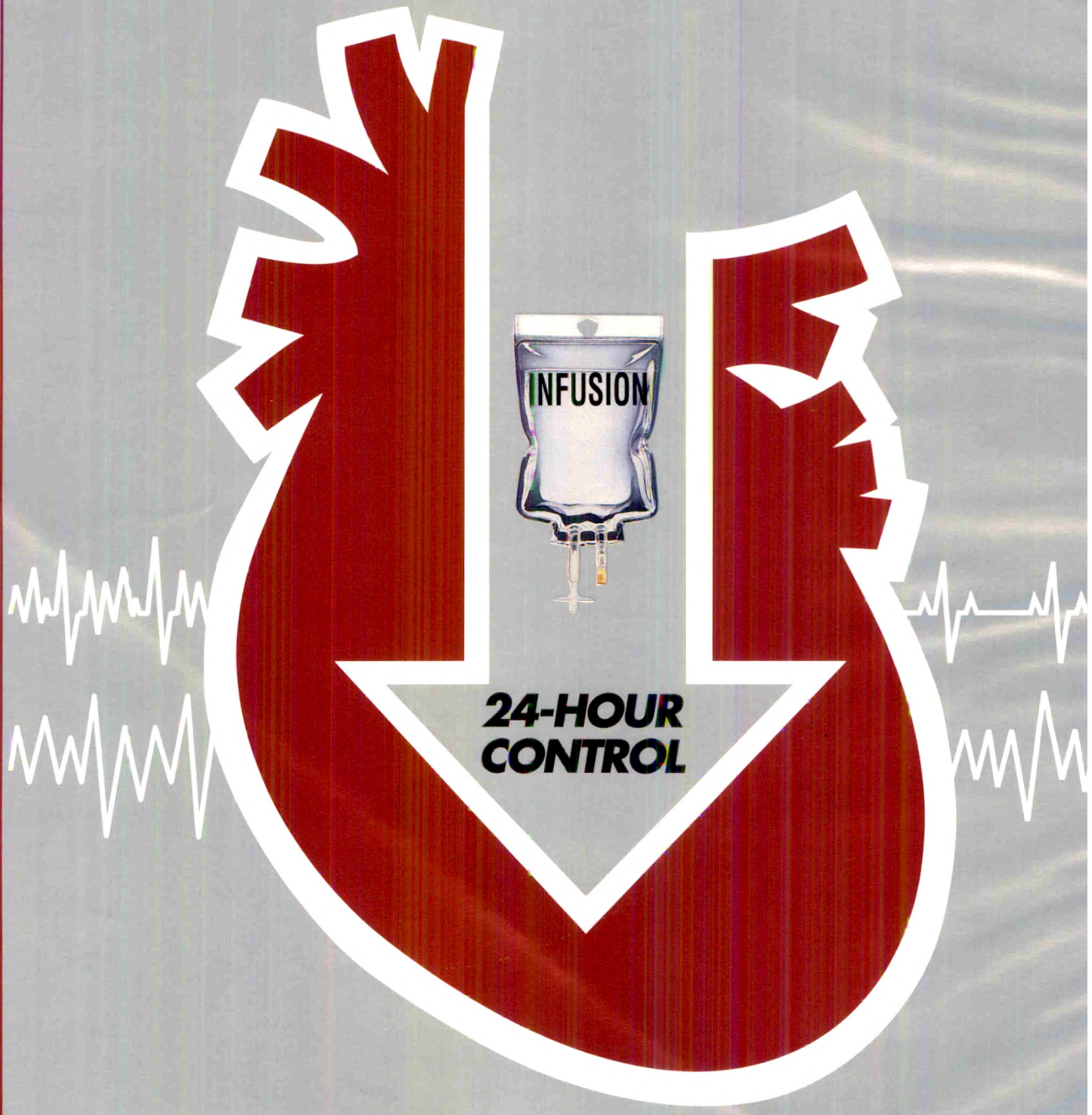
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Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; conversion to normal sinus rhythm is not greater than placebo.

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NEW CARDIZEM® Injectable

(diltiazem hydrochloride)

BOLUS / INFUSION



Should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

CIVXE461/A3318

For heart rate control during atrial fibrillation and flutter

MAINTAINS HEART RATE CONTROL SAFELY

FAST

- 3-minute onset of action from first bolus injection[1]
- 95% response rate within 2 to 7 minutes of administration[1]
- 1- to 3-hour duration of action with initial bolus

SAFE

- 4.3% incidence of asymptomatic hypotension[1]*
- 3.2 % incidence of symptomatic hypotension[1]*
- 3.9% incidence of injection site reaction[1]
- 1.7% incidence of flushing[1]*
- Little negative inotropic effect[1]†
- Not to be used in patients with WPW and short PR syndrome

  Other contraindications: sick sinus syndrome and second- or third-degree AV block, except with a functioning pacemaker; severe hypotension and shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

CONTINUOUS CONTROL

- Heart rate control through infusion for up to 24 hours[1,2]

  Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; conversion to normal sinus rhythm is not greater than placebo.

*Occurs most often during or immediately following bolus injection.
†Caution should be used in patients with congestive heart failure.

CARDIZEM INJECTABLE
Heart rate control that is fast, safe, and continuous

Please see brief summary of prescribing information on next page.

0763S1

NEW

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION

CONVENIENT DOSAGE

1	2	3
Beginning treatment as	If response is inadequate, wait 15 minutes	Treatment as
BOLUS: 0.25 mg/kg actual body weight over 2 minutes	**BOLUS:** 0.35 mg/kg actual body weight over 2 minutes	**INFUSION: 10* to 15 mg/hr** *5 mg/hr may be appropriate starting infusion for some patients.
20 mg average patient	**25 mg average patient**	

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

References: 1. Data on file, Marion Merrell Dow Inc.
2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

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CORONARY ARTERY DISEASE

977

Interrelation of Left Ventricular Ejection Fraction, Pulmonary Congestion and Outcome in Acute Myocardial Infarction

Shmuel Gottlieb, Arthur J. Moss, Michael McDermott, and Shirley Eberly

The interrelation between pulmonary congestion (none, mild or moderate, or severe) evaluated by chest roentgenogram in the coronary care unit, predischarge left ventricular (LV) ejection fraction (EF) (≥40%, 25 to 39% or <25%) and long-term prognosis was studied in 1,850 surviving patients of acute myocardial infarction. Cardiac mortality during a mean 2-year follow-up was 11.5%, and was related to both predischarge LVEF impairment and severity of pulmonary congestion. Cardiac mortality hazard ratios for LVEF of <25% and 25 to 39% were 5.32 (95% confidence intervals [CI] 3.49, 8.13; $p < 0.0001$) and 2.91 (CI 2.10, 4.02; $p < 0.0001$), respectively. Development of pulmonary congestion significantly augments the cardiac mortality risk derived from LVEF, with a marked mortality effect in patients with severe pulmonary congestion (hazard ratio 4.20; 95% CI 2.67, 6.62; $p < 0.0001$). These findings emphasize the independent prognostic role of pulmonary congestion and highlight the interactive mechanisms (systolic and diastolic dysfunctions) responsible for unfavorable outcome in surviving patients of acute myocardial infarction.

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Long-Term Prognosis After Acute Myocardial Infarction in Patients with Left Ventricular Hypertrophy on the Electrocardiogram

Solomon Behar, Henrietta Reicher-Reiss, Edward Abinader, Jacob Agmon, Jacob Barzilai, Yaacov Friedman, Elieser Kaplinsky, Nissim Kauli, Yehezkiel Kishon, Abraham Palant, Benyamin Peled, Leonardo Reisin, Zwi Schlesinger, Izhar Zahavi, Monty Zion, Uri Goldbourt, and the SPRINT Study Group

Among 4,720 consecutive survivors from acute myocardial infarction (AMI), the estimated prevalence of electrocardiographic left ventricular (LV) hypertrophy was 6.1%. The prevalence of electrocardiographic LV hypertrophy increased with age and was higher in patients with previous AMI, angina and systemic hypertension. The hospital course of patients with electrocardiographic LV hypertrophy was more complicated than in those without this finding and, more particularly, the former group had a

Continued on page A18

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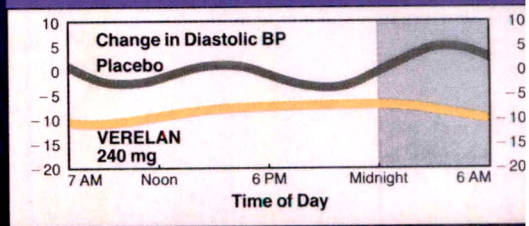
VERELAN®

Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES

P ROTECTS your hypertensive patient for 24 hours[1]

In cases studied, results of 24-hour ambulatory BP monitoring. VERELAN dosed 240 mg/day (n = 15); placebo (n = 10).[1]



R EDUCES wide variations in BP control[2]

N EGLIGIBLE discontinuation due to side effects[1]

D OSED once daily at all doses

Constipation, which can easily be managed in most patients, is the most frequently reported side effect of verapamil.

Please see brief summary of Prescribing Information including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS on adjacent page.

Lederle LEDERLE LABORATORIES
A Division of American Cyanamid Company
Wayne, New Jersey 07470

ADVANTUS Pharmaceuticals

WYETH-AYE LABORATOR



References: 1. Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol.* 1991;31:144-150. 2. Data on file for VERELAN 240 mg, Lederle Laboratories, Pearl River, NY.

Brief Summary

VERELAN®
Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can

VERELAN® verapamil HCl

increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extraren ance of digitoxin. The digoxin dose should be reduced when verapamil is given and the patient monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-l agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil admini Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, duction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertroj diomyopathy should be avoided, since significant hypotension may result. Verapamil has bee concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interac tween cimetidine and chronically administered verapamil has not been studied. In healthy volunteer ance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may re lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may redu pamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase se els of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuro lar blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate ani cinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic poter verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate a controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delive clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued duri pamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been esta

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequ ported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); sia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates grea 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); he (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1. block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNI**

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open tria keting experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atriov lar dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), s **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic ar phatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibriu ders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Resp** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** mastia, impotence, increased urination, spotty menstruation.

R 2

Lederle

Manufactured for
LEDERLE LABORATORIES DIVISION
American Cyanamid Company
Pearl River, NY 10965

by ELAN PHARMACEUTICAL RESEARCH CORP.
Gainesville, GA 30501

ADVANTUS Pharmaceuticals

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SAMPLE AND LITERATURE AVAILABLE UPON REQUEST

INDICATIONS:
HYPOMAGNESEMIA, MAGNESIUM DEFICIENCIES and/or MAGNESIUM DEPLETION *resulting from diuretic and/or digitalis therapy*[1], alcoholism[2], Cisplatin[3], Amphotericin B[4], Cyclosporin[5], perenteral nutrition[6], mannitol[7], Aminoglycosides[8], and diets low in Magnesium.

Note: May aid in preventing Calcium Oxaluria

SYMPTOMS: Refractory Hypokalemia, Tremors, and cramping of extremities and tongue, grimaces, myoclonic jerks, Chvostek's sign, ataxia, irritability, disorientation, convulsion, psychotic behavior.

CAUTION: Magnesium should be used with caution in renal insufficiency. If aperient, reduce dosage.

BLAINE CO INC

Blaine Co., Inc.
1465 Jamike Lane
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Phone: (606) 283-9437

References

1. Ryan M.P., Ph.D.: POTASSIUM/MAGNESIUM DEPLETION: IS YOUR PATIENT AT RISK OF SUDDEN DEATH? The American Journal of Medicine March, 20, 1987, Vol. 82 (Suppl 3A)

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7. Nanj A.A., DRUG-INDUCED ELECTROLYTE DISORDERS. Drug Intell. Clin. Pharm. 1983; 17:175-81.

8. ibid.

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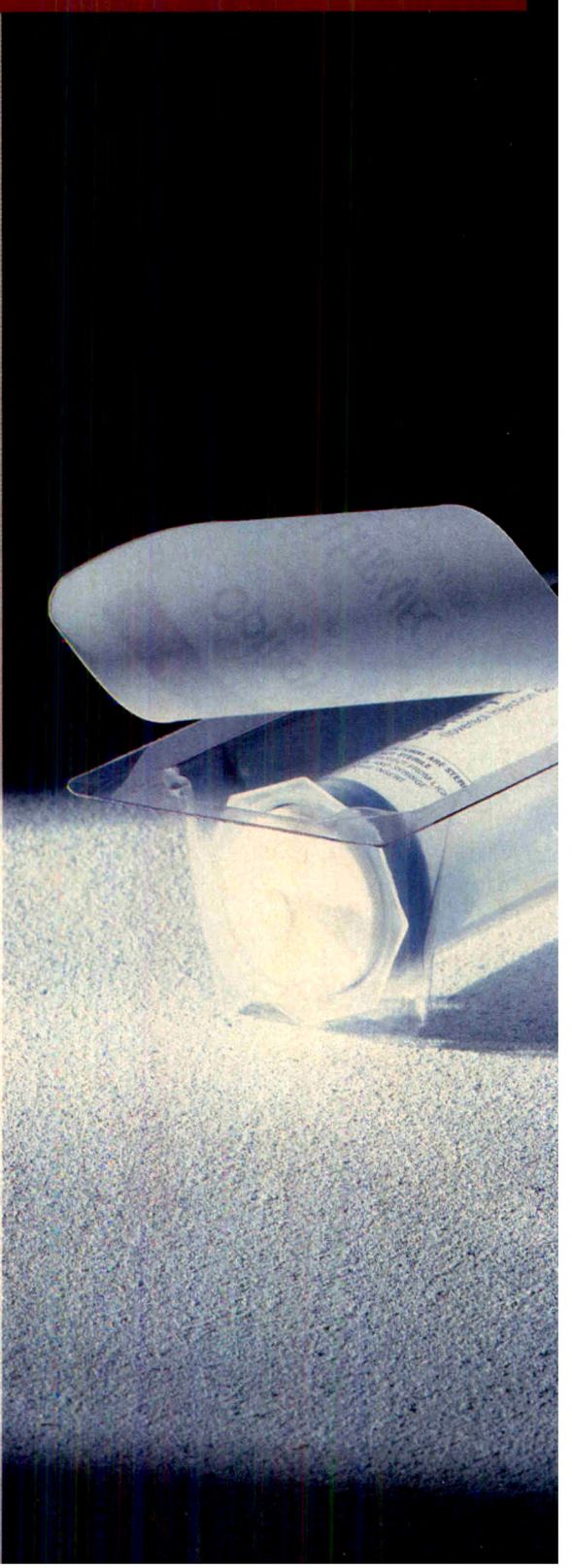
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*Hamilton G. Contamination of contrast agents by rubber components of 50-ml disposable syringes. *Radiology*. 1984;152:539-540.

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higher rate of congestive heart failure. The 1- and 5-year postdischarge mortality rates were significantly higher in patients with than without electrocardiographic LV hypertrophy. Multivariate analysis indicated that electrocardiographic LV hypertrophy is an independent predictor for increased subsequent post-AMI mortality.

991

Milwaukee Prehospital Chest Pain Project — Phase I: Feasibility and Accuracy of Prehospital Thrombolytic Candidate Selection

Tom P. Aufderheide, Michael H. Keelan, Gail E. Hendley, Nancy A. Robinson, Thomas E. Hastings, Ruben F. Lewin, Harvey F. Hewes, Alan Daniel, David Engle, Barry K. Gimbel, Kenneth R. Bortin, David J. Clardy, Donald H. Schmidt, Tanvir Bajwa, Peter Holzhauer, Russell C. Dabrowski, Gregory H. Schuchard, and Sam Teichman

A prospective clinical investigation was accomplished to determine the feasibility and accuracy of prehospital thrombolytic therapy candidate selection by base station emergency physicians. Paramedics acquired and transmitted prehospital 12-lead electrocardiograms (ECGs) and then applied a thrombolytic contraindication checklist. Using this information, emergency physicians selected candidates for thrombolytic therapy. No prehospital thrombolytic therapy was administered in this study. A safety committee of cardiologists independently determined base physician accuracy. Of 439 adult prehospital patients with prehospital chest pain, 91 (21%) had the final diagnosis of acute myocardial infarction (AMI), 38 (8.7%) had diagnostic prehospital ECGs, and 12 (2.7%) were selected as candidates for thrombolytic therapy. Seventy percent of patients with AMI had checklist exclusions for thrombolytic therapy. Prehospital evaluation increased mean scene time by 4 minutes. The median time from chest pain onset to paramedic arrival in patients with AMI was 60 minutes. The estimated mean time saved if prehospital thrombolytic therapy had been available was 101 ± 81 minutes. The safety committee concluded that acceptable accuracy of emergency physician prehospital electrocardiographic interpretation, checklist and case selection was achieved. Thus, emergency physicians can accurately identify candidates for prehospital thrombolytic therapy.

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Effect on Global and Regional Left Ventricular Functions by Percutaneous Transluminal Coronary Angioplasty in the Chronic Stage After Myocardial Infarction

Thomas Linderer, Bettina Guhl, Christoph Spielberg, Werner Wunderlich, Luise Schnitzer, and Rolf Schröder

In a group of 145 patients with successful percutaneous transluminal coronary angioplasty (PTCA) of the infarct-related artery late (5 ± 6 months) after myocardial infarction, ejection fraction improved in the long-term (7 ± 4 months) from 60 ± 13% to 64 ± 13% ($p < 0.001$), and left ventricular (LV) regional wall motion abnormalities were reduced by 40%. Multivariate discriminant analysis identified a reduced LV function (baseline ejection fraction <60%: ejection fraction from 48 ± 9% to 57 ± 14%, $p < 0.001$) and a high degree of stenosis before PTCA as predictors

Continued on page A23



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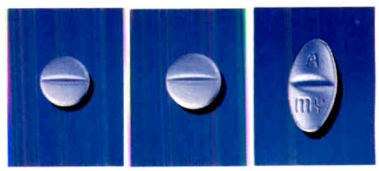
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- When given at 50 mg once daily, TOPROL XL lowers blood pressure 24 hours post-dosing[1]



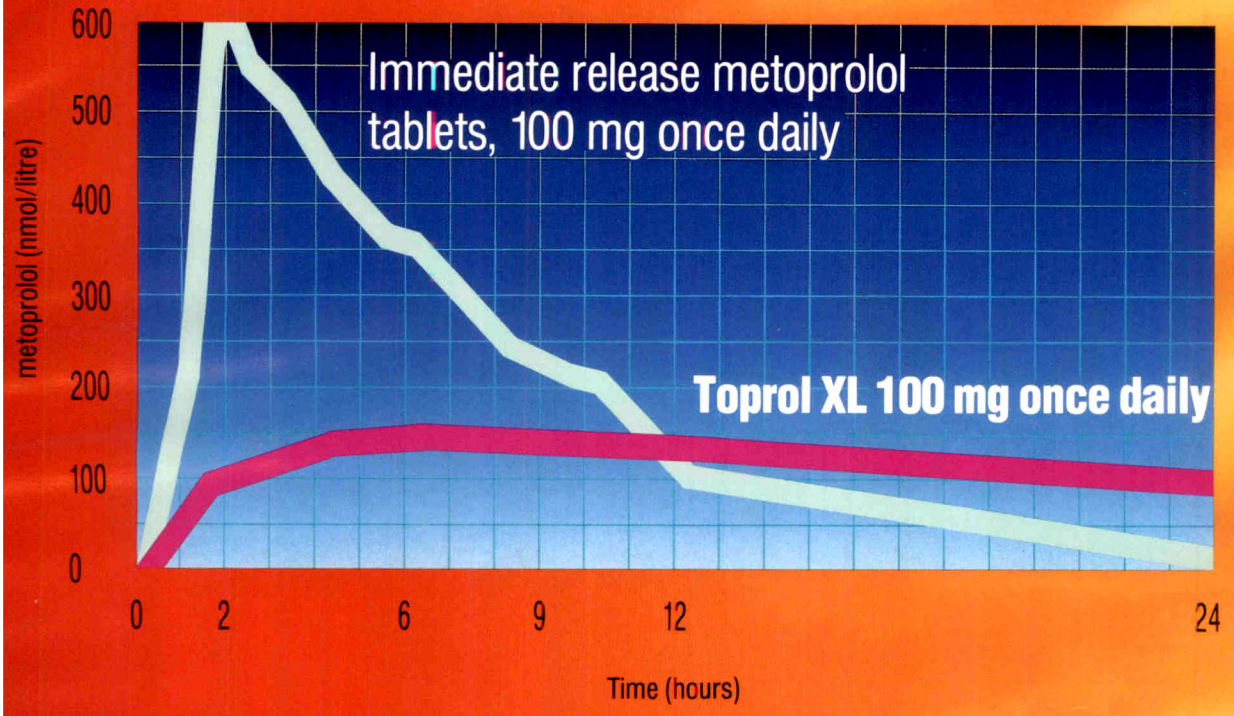
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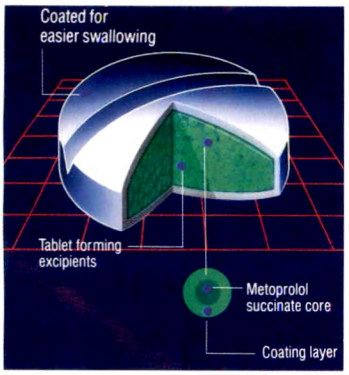
*indicated for hypertension and angina

New TOPROL XL for compliance and 24-hour coverage.



TOPROL XL maintains an even plasma level over 24 hours.

Graph reproduced with revisions and permission from Sandberg et al.[2]



The TOPROL XL delivery system releases metoprolol at a controlled and predictable rate[1]

- TOPROL XL is a proprietary formulation that provides the benefits of extended release tablets
- TOPROL XL has been used in over 1,000,000 patient-years worldwide[3]

Please see full prescribing information on following page.

TOPROL XL™ TABLETS

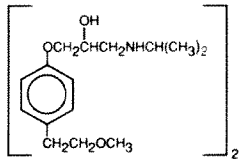
(Metoprolol succinate)

Extended Release Tablets

Tablets: 50 mg, 100 mg, and 200 mg

DESCRIPTION

Toprol XL, metoprolol succinate, is a $beta_1$-selective (cardioselective) adrenoceptor blocking agent, for oral administration, available as extended release tablets. Toprol XL has been formulated to provide a controlled and predictable release of metoprolol over once daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 47.5 mg, 95 mg and 190 mg of metoprolol succinate equivalent to 50, 100 and 200 mg of metoprolol tartrate, USP, respectively. Its chemical name is (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2propanol succinate (2:1) (salt). Its structural formula is:



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane. Inactive ingredients: Silicone dioxide, Cellulose compounds, Acetyltributyl citrate, Maize starch, Lactose powder, Polyvidone, Magnesium stearate, Polyethylene glycol, Titanium dioxide, Paraffin.

CLINICAL PHARMACOLOGY

Metoprolol is a $beta_1$-selective (cardioselective) adrenergic receptor blocking agent. This preferential effect is not absolute, however, and at higher plasma concentrations, metoprolol also inhibits $beta_2$-adrenoreceptors, chiefly located in the bronchial and vascular musculature. Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much greater than required for beta-blockade. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

The relative $beta_1$-selectivity of metoprolol has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective beta-blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta-blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

In five controlled studies in normal healthy subjects, the same daily doses of Toprol XL and immediate release metoprolol were compared in terms of the extent and duration of $beta_1$-blockade produced. Both formulations were given in a dose range equivalent to 100–400 mg of immediate release metoprolol per day. In these studies, Toprol XL was administered once a day and immediate release metoprolol was administered once to four times a day. A sixth controlled study compared the $beta_1$-blocking effects of a 50 mg daily dose of the two formulations. In each study, $beta_1$-blockade was expressed as the percent change from baseline, in exercise heart rate following standardized submaximal exercise tolerance tests at steady state. Toprol XL administered once a day, and immediate release metoprolol administered once to four times a day, provided comparable total $beta_1$-blockade over 24 hours (area under the $beta_1$-blockade versus time curve) in the dose range 100-400 mg. At a dosage of 50 mg once daily, Toprol XL produced significantly higher total $beta_1$-blockade over 24 hours than immediate release metoprolol. For Toprol XL, the percent reduction in exercise heart rate was relatively stable throughout the entire dosage interval and the level of $beta_1$-blockade increased with increasing doses from 50 to 300 mg daily. The effects at peak/trough (i.e. at 24 hours post dosing) were; 14/9, 16/10, 24/14, 27/22 and 27/20% reduction in exercise heart rate for doses of 50, 100, 200, 300 and 400 mg Toprol XL once a day, respectively. In contrast to Toprol XL immediate release metoprolol given as a dose of 50–100 mg once a day, produced a significantly larger peak effect on exercise tachycardia, but the effect was not evident at 24 hours. To match the peak to trough ratio obtained with Toprol XL over the dosing range of 200 to 400 mg, a t.i.d. to q.i.d. divided dosing regimen was required for immediate release metoprolol.

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using the E_{max} model, the maximal $beta_1$-blocking effect has been estimated to produce a 28.3% reduction in exercise heart rate. $Beta_1$-blocking effects in the range of 30–80% of the maximal effect (corresponding to approximately 8–23% reduction in exercise heart rate) are expected to occur at metoprolol plasma concentrations ranging from 30–540 nmol/L. The concentration-effect curve begins reaching a plateau between 200–300 nmol/L, and higher plasma levels produce little additional $beta_1$-blocking effect. The relative $beta_1$-selectivity of metoprolol diminishes and blockade of $beta_2$-adrenoceptors increases at higher plasma concentrations.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta-blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Hypertension

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

In controlled clinical studies, an immediate release dosage form of metoprolol has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics at dosages of 100–450 mg daily. Toprol XL dosages of 100 to 400 mg once daily, has been shown to possess comparable $beta_1$-blockade as conventional metoprolol tablets administered two to four times daily. In addition, Toprol XL administered at a dose of 50 mg once daily has been shown to lower blood pressure 24-hours post-dosing in placebo controlled studies. In controlled, comparative, clinical studies, immediate release metoprolol appeared comparable as an antihypertensive agent to propranolol, methyldopa, and thiazide-type diuretics, and to be effective both in supine and standing positions. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to drug plasma concentration, selection of proper dosage requires individual titration.

Angina Pectoris

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

In controlled clinical trials, an immediate release formulation of metoprolol has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 300 mg daily. Toprol XL, in dosages of 100 to 400 mg once daily, has been shown to possess comparable $beta_1$-blockade as conventional metoprolol tablets administered two to four times daily.

Pharmacokinetics

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration of conventional metoprolol tablets, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine, the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. Following intravenous administration of metoprolol, the urinary recovery of unchanged drug is approximately 10%. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

In comparison to conventional metoprolol, the plasma metoprolol levels following administration of Toprol XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once daily administration of Toprol XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Toprol XL, across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24 hour dosing interval, $beta_1$-blockade is comparable and dose-related (see CLINICAL PHARMACOLOGY). The bioavailability of metoprolol shows a dose-related, although not directly proportional increase with dose and is not significantly affected by food following Toprol XL administration.

INDICATIONS AND USAGE

Hypertension

Toprol XL tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Toprol XL tablets are indicated in the long-term treatment of angina pectoris.

CONTRAINDICATIONS

Hypertension and Angina

Toprol XL is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

Hypertension and Angina

Cardiac Failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Toprol XL should be administered cautiously. Both digitalis and Toprol XL slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Toprol XL should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative $beta_1$-selectivity, however, Toprol XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$-selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol XL should be used (see DOSAGE AND ADMINISTRATION).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Toprol XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Toprol XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PRECAUTIONS

General

Toprol XL should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Toprol XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Toprol XL without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol XL.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol XL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Risk Of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient. The following adverse reactions have been reported for metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol XL.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

No overdosage has been reported with Toprol XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since Toprol XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to Toprol XL.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly. On the basis of the pharmacologic actions of metoprolol tartrate the following general measures should be employed.

Elimination of the Drug. Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A $beta_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Toprol XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to Toprol XL, the same total daily dose of Toprol XL should be used.

As with immediate release metoprolol, dosages of Toprol XL should be individualized and titration may be needed in some patients.

Hypertension

The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Angina Pectoris

The dosage of Toprol XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).

HOW SUPPLIED

Tablets 50 mg:
Contain 47.5 mg of metoprolol succinate equivalent to 50 mg of metoprolol tartrate, USP
Are white, biconvex, round, film-coated
Engraved $\overset{A}{mo}$ on one side and scored on the other

Bottles of 100 NDC 0186-1098-05

Tablets 100 mg:
Contain 95 mg of metoprolol succinate equivalent to 100 mg of metoprolol tartrate, USP
Are white, biconvex, round, film-coated
Engraved $\overset{A}{ms}$ on one side and scored on the other

Bottles of 100 NDC 0186-1092-05

Tablets 200 mg:
Contain 190 mg of metoprolol succinate equivalent to 200 mg of metoprolol tartrate, USP
Are white, biconvex, oval, film-coated
Engraved $\overset{A}{my}$ and scored on one side

Bottles of 100 NDC 0186-1094-05

Store at controlled room temperature 15°-30°C (59°-86°F)

Manufactured by:
Astra Pharmaceutical Production, AB
Södertälje, Sweden

Manufactured for:

ASTRA® | Astra Pharmaceutical Products, Inc.
Westborough, MA 01581-4500

iss. 11/91

FOOTNOTES:

1. Please see full prescribing information above.
2. Sandberg A, Blomqvist I, Jonsson UE, Lundborg P, Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol; a comparison with conventional tablets. Eur J Clin Pharmacol 1988; 33 (Suppl): S9-S14.
3. Data on file at AB Hassle.

of improvement in LV function. It is concluded that PTCA, even months after acute myocardial infarction, can improve chronic ischemic LV dysfunction, especially in patients with more severely reduced LV function.

1003

Circadian Distribution of Onset of Acute Myocardial Infarction in Subgroups from Analysis of 10,791 Patients Treated in a Single Center

Ole Hansen, Bengt W. Johansson, and Bo Gullberg

A circadian variation of symptom onset in acute myocardial infarction (AMI) with an increased frequency in the late morning and possibly also in the evening has been found in several studies. It has been suggested, however, that different circadian rhythms may exist in various subgroups of patients. This possibility was examined in a population of 10,791 patients collected between 1973 and 1987 in a continuously operating register of myocardial infarction in Malmö, Sweden. Bimodal circadian rhythms were found in all defined subgroups, except in patients taking cardioselective β blockers before their AMI. Statistically significant interactions were found between symptom onset and age dichotomized at 70 years, and patients with and without a history of previous AMI. In a multivariate analysis only these 2 variables (age $\leq/>70$ years; $\pm$ history of a previous myocardial infarction) were found to modify the circadian rhythm of symptom onset in the population. It is suggested that only minor differences in symptom onset between various subgroups exist within the same population, and that these differences probably are unable to explain differences in circadian rhythm of symptom onset between different populations.

1009

Effects of Left Ventricular Dysfunction on the Circadian Variation of Ventricular Premature Complexes in Healed Myocardial Infarction

Anne M. Gillis, Robert W. Peters, L. Brent Mitchell, Henry J. Duff, Margot McDonald, and D. George Wyse

The effect of left ventricular dysfunction on the circadian variation of ventricular premature complex (VPC) frequency was evaluated in 132 patients with depressed ventricular function after myocardial infarction. In patients with left ventricular ejection fraction (LVEF) ≤ 0.30, a distinct circadian variation of VPCs, and the expected morning increase in VPC frequency were absent. A circadian variation of VPC frequency was also absent in patients with severe symptomatic congestive heart failure and in those receiving β-adrenoceptor blocking agents. The relation between heart rate and VPC frequency was also altered in these patients. A lower proportion of patients with LVEF ≤ 0.30 (26%) manifested a positive correlation between heart rate and VPC frequency than did those with LVEF >0.30 (46%) ($p < 0.05$). The mechanism of this altered circadian rhythm needs further investigation.

1015
Comparison of the Plasma Levels of Apolipoproteins B and A-1, and Other Risk Factors in Men and Women with Premature Coronary Artery Disease
Peter O. Kwiterovich, Jr., Josef Coresh, Hazel H. Smith, Paul S. Bachorik, Carol A. Derby, and Thomas A. Pearson

The association of age, smoking, hypertension, obesity, diabetes, positive family history of premature coronary artery disease (CAD), and plasma levels of cholesterol, triglyceride, lipoproteins and apolipoproteins (apoA-1 and 2, and B, respectively) were examined in 203 patients (99 men aged ≤50 years, and 104 women aged ≤60 years) undergoing elective diagnostic coronary arteriography. In men, age, smoking, and triglyceride and apoA-1 levels were independently associated with CAD. In women, smoking and plasma apoB levels were the strongest variables independently associated with CAD. "Nontraditional" risk factors (plasma apoA-1 and apoB levels) were better predictors of premature CAD than were plasma lipoproteins. Smoking was the strongest of the traditional nonlipid risk factors. The differences in the etiology of premature CAD between men and women needs further study.

1022
Prognostic Importance of Quantitative Analysis of Coronary Cineangiograms
G. B. John Mancini, Martial G. Bourassa, Paula R. Williamson, Guy Leclerc, Scott F. DeBoe, Bertram Pitt, and Jacques Lesperance

Numerous studies have demonstrated the prognostic value of cineangiographic data. Few analyses have examined quantitative parameters of wall motion and shape or coronary stenosis severity. To determine the prognostic importance of quantitative parameters, baseline cineangiograms of 283 patients with a mean of 8.3 years of clinical follow-up were subjected to quantitative analyses. Regional shape (anterior and inferior walls) and motion (anterior wall only) indexes, when considered in isolation, were predictive of event-free survival. These parameters were not of independent prognostic importance in regression models. The most important independent predictors of overall cardiac mortality or an initial lethal cardiac event were the ejection fraction and the percent diameter narrowing of each of the major coronary arteries. Myocardial infarction, however, was predicted by the percent diameter stenosis of the left main and left anterior descending arteries but not the ejection fraction. Thus, quantification of the ejection fraction and severity of coronary narrowings, but not indexes of regional function or shape are of independent prognostic importance.

Continued on page A26

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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1028
Supraventricular Tachycardia Mechanisms and Their Age Distribution in Pediatric Patients

Jae Kon Ko, Barbara J. Deal, Janette F. Strasburger, and D. Woodrow Benson, Jr., with the technical assistance of Mark Donovan

We examined age distribution of supraventricular tachycardia (SVT) mechanisms in 137 nonsurgically treated infants, children and adolescents. An electrophysiologic study was performed in each patient: transesophageal (110 patients) or transvenous (14 patients), or both (13 patients). Mechanisms were classified as SVT using accessory atrioventricular (AV) connections, primary atrial tachycardia, and tachycardia due to reentry within the AV node. Mechanisms of SVT appear to be age-dependent. The age-dependent probability of SVT using accessory connection is 58 to 84% and is most common in infants. Primary atrial tachycardias are distributed throughout childhood with a probability of 11 to 16%. It is speculated that the propensity to tachycardia due to reentry within the AV node occurs during postnatal development because it has an age-dependent probability of 0 to 31% and rarely occurs before the second year of life.

1033
On the Mechanism of Termination and Perpetuation of Atrial Fibrillation

Yukio Asano, Jun-ichi Saito, Kazuo Matsumoto, Keiko Kaneko, Toshio Yamamoto, and Masatsugu Uchida

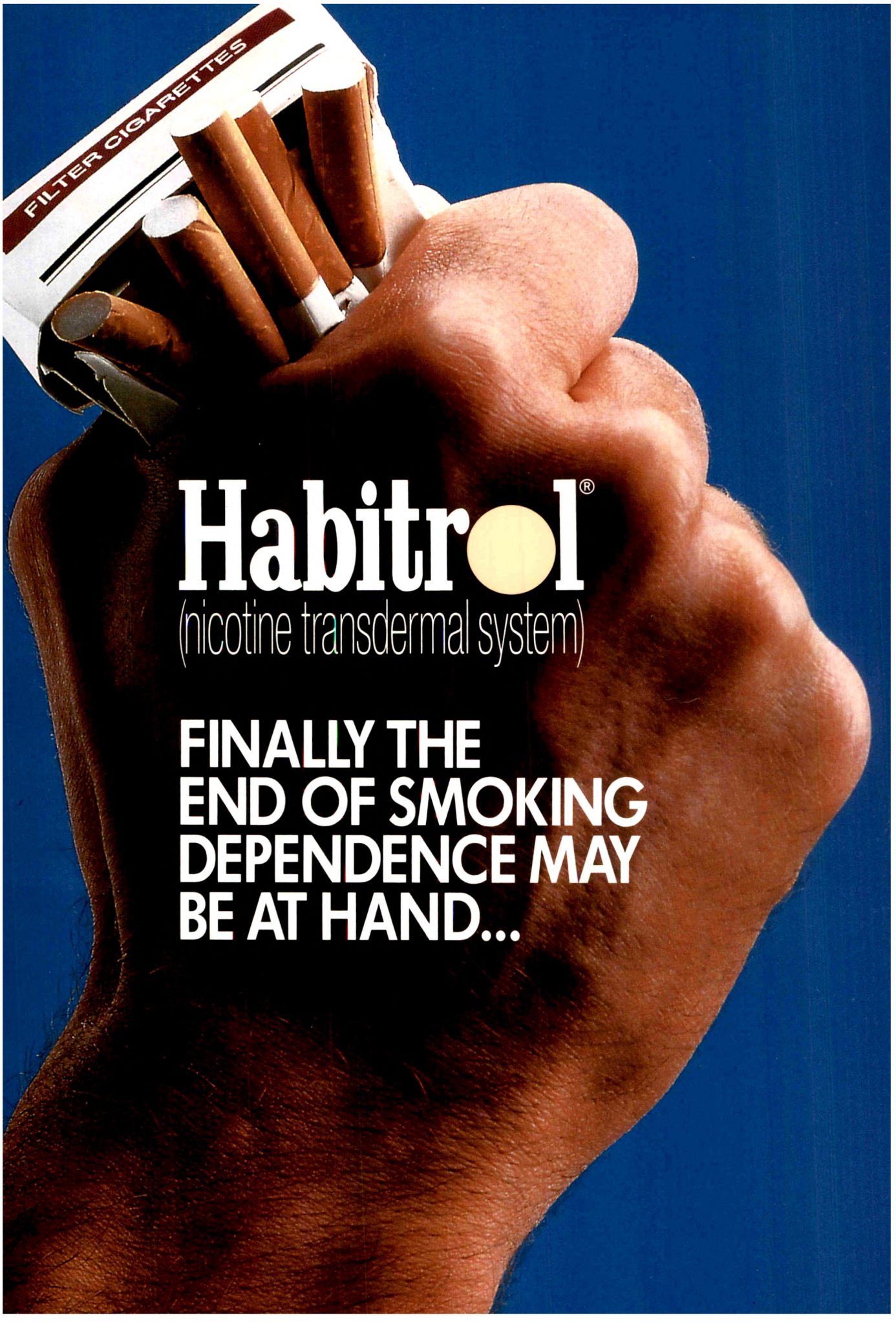
To clarify the mechanism of termination and perpetuation of atrial fibrillation (AF), the intraatrial potentials during AF were analyzed using the wavelength concept. The study group comprised 20 patients with transient AF (group 1) and 10 patients with sustained AF (group 2). Wavelength is the product of refractory period and conduction velocity. During AF, refractory period correlates with the mean interval between each intraatrial potential (mean ff) and conduction velocity correlates inversely with the width of intraatrial potentials (f width). Thus, the wavelength index was defined as (mean ff)/(mean f width). Group 1 had higher wavelength indexes after AF induction than group 2 ($p < 0.05$). In group 1, wavelength indexes increased just before AF termination ($p < 0.001$). In 3 group 2 patients, AF stopped after disopyramide infusion, whereas wavelength indexes increased before AF ended ($p < 0.05$). Thus, prolongation of the wavelength is essential for AF termination and shorter wavelengths are necessary for AF perpetuation.

1039
Long-Term Outcome of Paced and Nonpaced Patients with Severe Carotid Sinus Syndrome

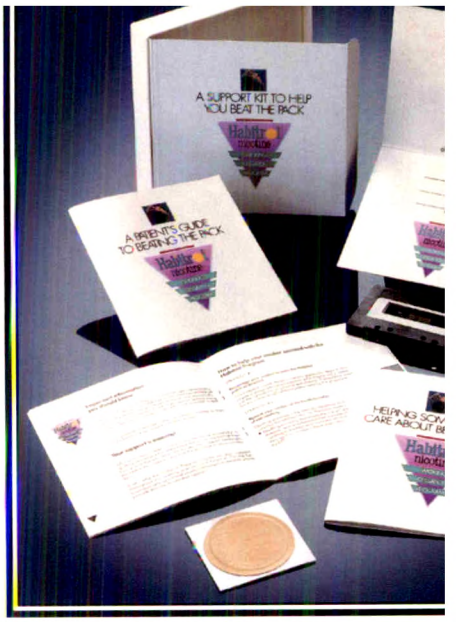
Michele Brignole, Carlo Menozzi, Gino Lolli, Nicola Bottoni, and Germano Gaggioli

A randomized, prospective study comparing pacemaker therapy and no therapy was performed in 60 patients affected by severely symptomatic

Continued on page A32


FILTER CIGARETTES
Habitrol®
(nicotine transdermal system)
FINALLY THE
END OF SMOKING
DEPENDENCE MAY
BE AT HAND...

For the motivated patient who wants to quit



Habitrol®

(nicotine transdermal system)

Habitrol significantly increases abstinence rates* when used as part of a comprehensive behavioral smoking cessation program—even in moderately to highly nicotine-dependent patients[1†]

- Significantly reduces craving for cigarettes through controlled nicotine release[1]
- Helps break the chain of smoking dependence with full 24-hour nicotine plasma levels
- Safe and well tolerated
- Provides the safety of child-resistant packaging

Habitrol is available with a Patient Support Kit, to be used as part of a comprehensive behavioral smoking cessation program. This kit provides materials to help motivated patients address the behavioral and social components of smoking dependence.

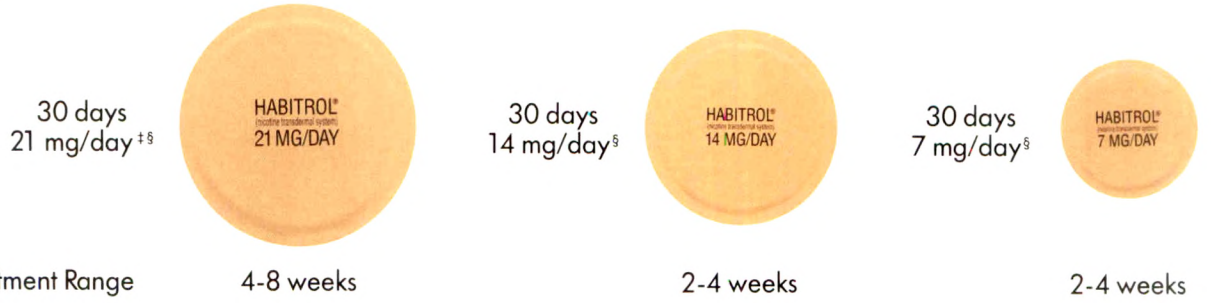
This product should not be used for more than three months. The effects of Habitrol treatment on fetal development are unknown. Pregnant or nursing smokers should be encouraged to attempt smoking cessation using nonpharmacologic approaches before using Habitrol. The risks vs. benefits of nicotine replacement should be weighed in patients with certain cardiovascular and peripheral vascular diseases. Certain concomitant medications may need dosage adjustments (see Drug Interactions section of complete Prescribing Information).

THE PATCH THAT BEATS THE PACK



Helps patients adjust to a smokefree lifestyle with gradual reduction of nicotine

- Available in three dosages for step-down therapy
- Start most patients on one 21 mg/day patch for 30 days, continue with one 14 mg/day patch for 30 days, and follow with one 7 mg/day patch for 30 days‡



Treatment Range	4-8 weeks	2-4 weeks	2-4 weeks

- Used and unused systems should be kept out of the reach of children and pets



*Abstinence was measured by diary entries and confirmed by breath carbon monoxide levels.
†Represents patients scoring ≥6 points on the Fagerstrom Tolerance Test
‡For patients with coronary artery disease or who weigh less than 100 lbs or smoke less than ½ pack of cigarettes/day, please see Individualization of Dosage Section of Prescribing Information
§Patches shown 50% of actual size

Please see brief summary of Prescribing Information on next page.

Habitrol®

(nicotine transdermal system)
Systemic delivery of 21, 14, or 7 mg/day over 24 hours

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Habitrol treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Habitrol treatment should be used as a part of a comprehensive behavioral smoking cessation program.

The use of Habitrol systems for longer than 3 months has not been studied.

CONTRAINDICATIONS

Use of Habitrol systems is contraindicated in patients with hypersensitivity or allergy to nicotine or to any of the components of the therapeutic system.

WARNINGS

Nicotine from any source can be toxic and addictive. Smoking causes lung cancer, heart disease, emphysema, and may adversely affect the fetus and the pregnant woman. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking while using Habitrol systems, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy Warning

Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Habitrol treatment can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by Habitrol systems has not been examined in pregnancy (see PRECAUTIONS, Other Effects). Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If Habitrol therapy is used during pregnancy, or if the patient becomes pregnant while using Habitrol treatment, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children

The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if Habitrol systems are applied or ingested by children or pets. Used 21 mg/day systems contain about 60% (32 mg) of their initial drug content. Therefore, patients should be cautioned to keep both used and unused Habitrol systems out of the reach of children and pets.

PRECAUTIONS

General

The patient should be urged to stop smoking completely when initiating Habitrol therapy (see DOSAGE AND ADMINISTRATION). Patients should be informed that if they continue to smoke while using Habitrol systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the Habitrol dose should be reduced or Habitrol treatment discontinued (see WARNINGS). Physicians should anticipate that concomitant medications may need dosage adjustment (see Drug Interactions).

The use of Habitrol systems beyond 3 months by patients who stop smoking should be discouraged because the chronic consumption of nicotine by any route can be harmful and addicting.

Allergic Reactions: In a 6-week open-label dermal irritation and sensitization study of Habitrol systems, 22 of 220 patients exhibited definite erythema at 24 hours after application. Upon rechallenge, 3 patients exhibited mild-to-moderate contact allergy. Patients with contact sensitization should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking. In the efficacy trials, erythema following system removal was typically seen in about 17% of patients, some edema in 4%, and dropouts due to skin reactions occurred in 6% of patients.

Patients should be instructed to promptly discontinue the Habitrol treatment and contact their physicians if they experience severe or persistent local skin reactions at the site of application (e.g., severe erythema, pruritus or edema) or a generalized skin reaction (e.g., urticaria, hives, or generalized rash).

Skin Disease: Habitrol systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Cardiovascular or Peripheral Vascular Diseases: The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of Habitrol treatment was reported occasionally. If serious cardiovascular symptoms occur with Habitrol treatment, it should be discontinued.

Habitrol treatment should generally not be used in patients during the immediate post-myocardial infarction period, patients with serious arrhythmias, and patients with severe or worsening angina pectoris.

Renal or Hepatic Insufficiency: The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Endocrine Diseases: Habitrol treatment should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease: Nicotine delays healing in peptic ulcer disease; therefore, Habitrol treatment should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension: Nicotine constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Habitrol treatment should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for Patients

A patient instruction sheet is included in the package of Habitrol systems dispensed to the patient. It contains important information and instructions on how to use and dispose of Habitrol systems properly. Patients should be encouraged to ask questions of the physician and pharmacist.

Patients must be advised to keep both used and unused systems out of the reach of children and pets.

Drug Interactions

Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
Insulin	Increase of subcutaneous insulin absorption with smoking cessation
Adrenergic antagonists (e.g., prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation

May Require an Increase in Dose at Cessation of Smoking	Possible Mechanism
Adrenergic agonists (e.g., isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Nicotine and cotinine were not mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy Category D (see WARNINGS)

The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Habitrol treatment on fetal development are unknown. Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Habitrol treatment should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of use of nicotine replacement by the patient, who may continue to smoke.

Teratogenicity

Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg/day IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects

Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension (fetal and maternal concentrations were about 20 times those achieved after smoking 1 cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low-birthweight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters has been studied near term. Cigarettes increased fetal aortic blood flow and heart rate, and decreased uterine blood flow and fetal breathing movements. Habitrol treatment has not been studied in pregnant humans.

Labor and Delivery

Habitrol systems are not recommended to be left on during labor and delivery. The effects of nicotine on the mother or the fetus during labor are unknown.

Nursing Mothers

Caution should be exercised when Habitrol therapy is administered to nursing women. The safety of Habitrol treatment in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk-to-plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. The nicotine concentrations in milk can be expected to be lower with Habitrol treatment when used as directed than with cigarette smoking, as maternal plasma nicotine concentrations generally reduced with nicotine replacement. The risk of expo of the infant to nicotine from Habitrol systems should be wei against the risks associated with the infant's exposure to nic from continued smoking by the mother (passive smoke expo and contamination of breast milk with other componen tobacco smoke) and from Habitrol systems alone or in combin with continued smoking.

Pediatric Use

Habitrol systems are not recommended for use in children bec the safety and effectiveness of Habitrol treatment in children adolescents who smoke have not been evaluated.

Geriatric Use

Forty-eight patients over the age of 60 participated in clinical t of Habitrol therapy. Habitrol therapy appeared to be as effecti this age group as in younger smokers.

ADVERSE REACTIONS

Assessment of adverse events in the 792 patients who particip in controlled clinical trials is complicated by the occurrence and CNS effects of nicotine withdrawal as well as nicotine ex The actual incidences of both are confounded by concurrent s ing by many of the patients. In the trials when reporting adv events, the investigators did not attempt to identify the cause symptom.

Topical Adverse Events

The most common adverse event associated with topical nicot a short-lived erythema, pruritus, or burning at the applicatior which was seen at least once in 35% of patients on Habitrol t ment in the clinical trials. Local erythema after system remova noted at least once in 17% of patients and local edema in 4% thema generally resolved within 24 hours. Cutaneous hypers tivity (contact sensitization) occurred in 2% of patients on Hal treatment (see PRECAUTIONS, Allergic Reactions).

Probably Causally Related

The following adverse events were reported more frequen Habitrol-treated patients than in placebo-treated patier exhibited a dose response in clinical trials.

Digestive system – Diarrhea,* dyspepsia.*
Mouth/Tooth disorders – Dry mouth.
Musculoskeletal system – Arthralgia,† myalgia.*
Nervous system – Abnormal dreams,† somnolence.†

Frequencies for 21 mg/day system
*Reported in 3% to 9% of patients.
†Reported in 1% to 3% of patients.
Unmarked if reported in < 1% of patients.

Causal Relationship Unknown

Adverse events reported in Habitrol- and placebo-treated pa at about the same frequency in clinical trials are listed below clinical significance of the association between Habitrol trea and these events is unknown, but they are reported as ale information for the clinician.

Body as a whole – Allergy,† back pain.†
Cardiovascular system – Hypertension.†
Digestive system – Abdominal pain,† constipation,† nau vomiting.
Nervous system – Dizziness,* concentration impaired,† headache (17%), insomnia.*
Respiratory system – Cough increased,† pharyngitis,† sinusitis.†
Urogenital system – Dysmenorrhea.*

Frequencies for 21 mg/day system
*Reported in 3% to 9% of patients.
†Reported in 1% to 3% of patients.
Unmarked if reported in < 1% of patients.

DRUG ABUSE AND DEPENDENCE

Habitrol systems are likely to have a low abuse potential bas differences between it and cigarettes in four characteristics monly considered important in contributing to abuse: much s absorption, much smaller fluctuations in blood levels, lower levels of nicotine, and less frequent use (i.e. once daily).

Dependence on nicotine polacrilex chewing gum replac therapy has been reported. Such dependence might also from transference to Habitrol systems of tobacco-based ni dependence. The use of the system beyond 3 months has no evaluated and should be discouraged.

To minimize the risk of dependence, patients should be e aged to withdraw gradually from Habitrol treatment afte 8 weeks of usage. Recommended dose reduction is to progre decrease the dose every 2 to 4 weeks (see DOSAGE AND AD ISTRATION).

CAUTION: Federal law prohibits dispensing with[illegible] prescr

C91-37 (Rev.

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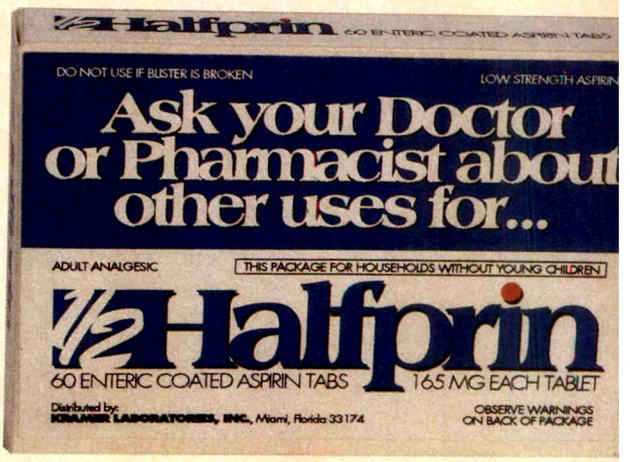
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Aspirin For Cardiology

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165 mg. enteric coated aspirin tablets

When low-strength aspirin is all your patients need to reduce the risk of recurrent Myocardial infarction... Unstable Angina



● COMPLIANCE ASSURED

Allows for flexible dosing. No need to break tablet in half or alternate the daily dose to achieve individualized dosing.

● ENTERIC COATED

Minimizes gastric irritation.

● CONVENIENCE

Low strength tablet preferred for flexible dosing.

● PROVEN SAFE & EFFECTIVE

*Recent studies have proven aspirin to be safe and effective in reducing the risk of recurrent heart attacks and unstable angina.**

* REFERENCES

1. N Engl J Med 1989;321:129-35. 2. Aust-Fam-Physician. 1990 Feb; 19(2)217221-3. 3. American Fam-Physician r. v43 p1431 April 91. 4. New Scientist v119 p24 Aug 25 88. 5. Health (N.Y., N.Y.) v20 p8 May88. 6. JAMA v257 p2134-5 April 24, 87. 7. N. Engl J Med v311 p1206-11 Nov. 8 84. 8.JAMA, July 24/31 V266 No. 4.

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carotid sinus syndrome. During 4-year follow-up, most nonpaced patients had recurrence of symptoms, which frequently led to the implant of a secondary pacemaker; paced patients had a significantly lower rate of symptom recurrence, and a better quality of life.

1044

Usefulness of Clinical Characteristics in Predicting the Outcome of Electrophysiologic Studies in Unexplained Syncope

William B. Bachinsky, Mark Linzer, Leisa Weld, and N. A. Mark Estes III

Clinical factors predicting the outcome of electrophysiologic studies in syncope would be helpful in determining which syncope patients would benefit from this test. This study validates the sensitivity and specificity of clinical predictors found in prior work to be highly sensitive for predicting electrophysiologic study results in syncope. Organic heart disease and nonsustained ventricular tachycardia on Holter monitoring were highly sensitive for ventricular tachycardia at electrophysiologic study (sensitivity 100%). Sinus bradycardia, first-degree atrioventricular block and bundle branch block were also sensitive for bradyarrhythmic outcomes (sensitivity 79%). Electrophysiologic testing in syncope is unlikely to be diagnostic in patients without these clinical variables.

VALVULAR HEART DISEASE

1050

Estimation of Mitral Valve Area from Regression Analysis of the Pressure Gradient in Mitral Stenosis

John A. Bittl, Alan C. Yeung, Vladimir Vekshtein, John D. Parker, and R. David Fish

Does the collapse of the mitral gradient in mitral stenosis correlate with mitral valve area (MVA)? In this study, linear and nonlinear regression analysis of mitral pressure tracings were equally accurate in yielding estimates that closely matched the Gorlin measurements of MVA. These results suggest that linear regression analysis of mitral gradient tracings may yield on-line estimates of MVA in the cardiac catheterization laboratory.

CONGENITAL HEART DISEASE

1056

Transcatheter Closure of Atrial Septal Defect by "Buttoned" Devices

P. Syamasundar Rao, Allen D. Wilson, and Paramjeet S. Chopra

Twelve patients underwent transcatheter closure of atrial septal defect with a new "buttoned" device that was delivered to the site of implantation with an 8Fr sheath. Four closures were performed with the first-generation device, and 8 with a modified, second-generation device. One of the first 4 devices got dislodged and needed surgical intervention. After modification of the device to include a radiopaque marker on the "button," no

Continued on page A36

Even in mild to moderate heart failure, when diuretics and digitalis are not enough*



ADDING CAPOTEN DOES MORE FOR PATIENTS SO THEY CAN DO MORE FOR THEMSELVES.[1,2]

IN HEART FAILURE

CAPOTEN®
(captopril)
12.5 mg, 25 mg, 50 mg, 100 mg Scored Tablets

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

***CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.**

Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

CAPOTEN® TABLETS
Captopril Tablets

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS: Angioedema–Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia/Agranulocytosis–Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease) neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS [Drug Interactions].) In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors, including CAPOTEN, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

Captopril crosses the human placenta. When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and/or death in the newborn. Oligohydramnios has also been reported, presumably representing decreased renal function in the fetus; limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation have been reported in association with oligohydramnios. Patients who do require ACE inhibitors during the second and third trimester of pregnancy should be apprised of the potential hazards to the fetus, and frequent ultrasound examinations should be performed to look for oligohydramnios. If oligohydramnios is observed, CAPOTEN should be discontinued unless it is considered life-saving to the mother.

Other potential risks to the fetus/neonate exposed to ACE inhibitors include: prematurity, patent ductus arteriosus; fetal death has also been reported. It is not clear, however, whether these reported events are related to ACE inhibition or the underlying maternal disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

Captopril was embryocidal in rabbits when given in doses about 2 to 70 times (on a mg/kg basis) the maximum recommended human dose, and low incidences of craniofacial malformations were seen. These effects in rabbits were most probably due to the particularly marked decrease in blood pressure caused by the drug in this species.

Captopril given to pregnant rats at 400 times the recommended human dose continuously during gestation and lactation caused a reduction in neonatal survival.

No teratogenic effects (malformations) have been observed after large doses of captopril in hamsters and rats.

If CAPOTEN is used during pregnancy or if the patient becomes pregnant while taking CAPOTEN, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: General: *Impaired Renal Function*–Hypertension–Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure–About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Hyperkalemia:* Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.) *Valvular Stenosis*–A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*–If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension–Patients on Diuretic Therapy*–Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity–In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release–Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity–The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium–Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis–Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Lithium–Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category D: See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use: Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less that that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension with captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials.

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality: In infants exposed *in utero* to ACE inhibitors the following adverse experiences have been reported: fetal and neonatal death, renal failure, hypoplastic lung development, hypotension, hyperkalemia, skull hypoplasia, limb contractures, craniofacial deformities, intrauterine growth retardation, prematurity and patent ductus arteriosus (see WARNINGS, Fetal/Neonatal Morbidity and Mortality).

Altered Laboratory Findings: *Serum Electrolytes: Hyperkalemia:* small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of: 12.5 mg in bottles of 100 and 1000; 25 mg in bottles of 100 and 1000; 50 mg in bottles of 100 and 1000; 100 mg in bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets.

(J3-658W)

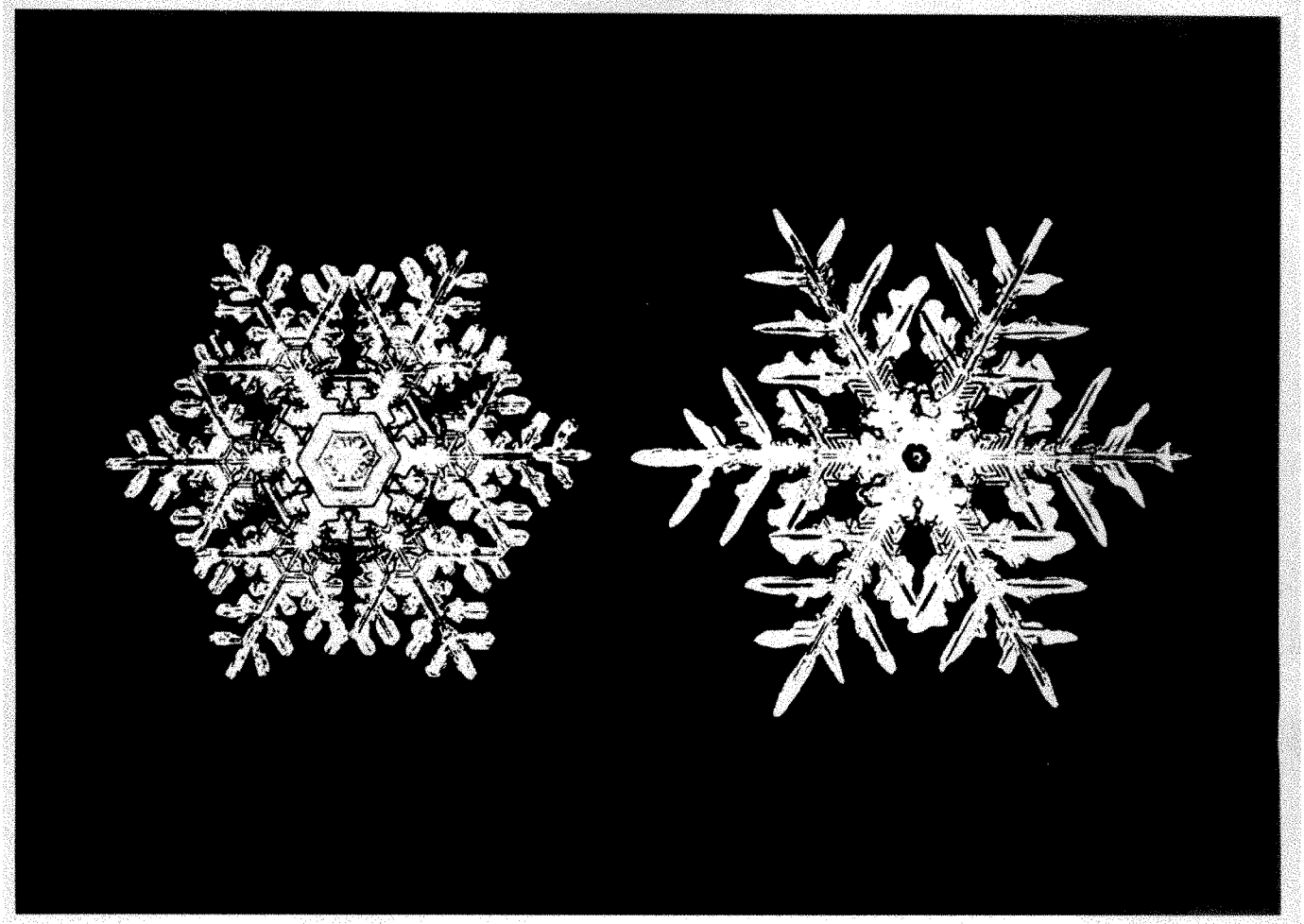
References: 1. The Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539-544, 1988. 2. Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *JACC* 2:755-763, 1983.

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0522-505

Issued: March 1992



No two are exactly alike.

Because body chemistry differs from person to person, we often need a choice of drugs to treat the same illness.

You've heard it said that no two snowflakes are exactly alike. The variety is endless. Much the same is true of the human body.

Take the case of two patients suffering from hypertension. Both under the care of the same physician, who prescribes the same medication for each. One patient responds to the medication while the other reports unpleasant side-effects. Thanks to the diversity of drugs available to treat this illness, the doctor is able to prescribe another medicine that works without the side effects.

To maintain the high standards of quality care, and because some drugs work better than others on different people, it is essential to have this diversity.

America's research-based pharmaceutical companies are committed to providing a wide range of drugs of the highest quality to serve the public. Why? Because the public is made up of different people requiring different treatment—even when they suffer from the same illness.

Pharmaceutical Manufacturers Association

IF A NEW MEDICINE CAN HELP, WE'RE WORKING ON IT.

device dislodgements were observed. Follow-up results were good. Based on these data, it is concluded that transcatheter closure with the buttoned device is safe and effective, and further clinical trials with this device are warranted.

MISCELLANEOUS

1063
Reversal of Endothelin-1-Induced Vasoconstriction by Nifedipine in Human Resistance Vessels in Vivo in Healthy Subjects

Wolfgang Kiowski and Lilly Linder

Brachial artery infusions of endothelin-1 in 10 healthy volunteers increased forearm blood flow during the first minute and decreased forearm blood flow during the third minute. Blockade of voltage-operated calcium channels by brachial artery infusions of nifedipine resulted in dose-dependent increases in forearm blood flow. Co-infusion of nifedipine and endothelin-1 completely abolished the vasoconstrictor effects of endothelin-1, and percent changes of forearm blood flow were similar to or greater than changes during nifedipine infusions. Luminally applied endothelin-1 has a transient vasodilator and a marked vasoconstrictor effect in human resistance vessels in vivo. The vasoconstrictor effect is effectively counteracted by blockade of voltage-operated calcium channels.

1067
Left Ventricular Dimensions and Mass Using Magnetic Resonance Imaging in Female Endurance Athletes

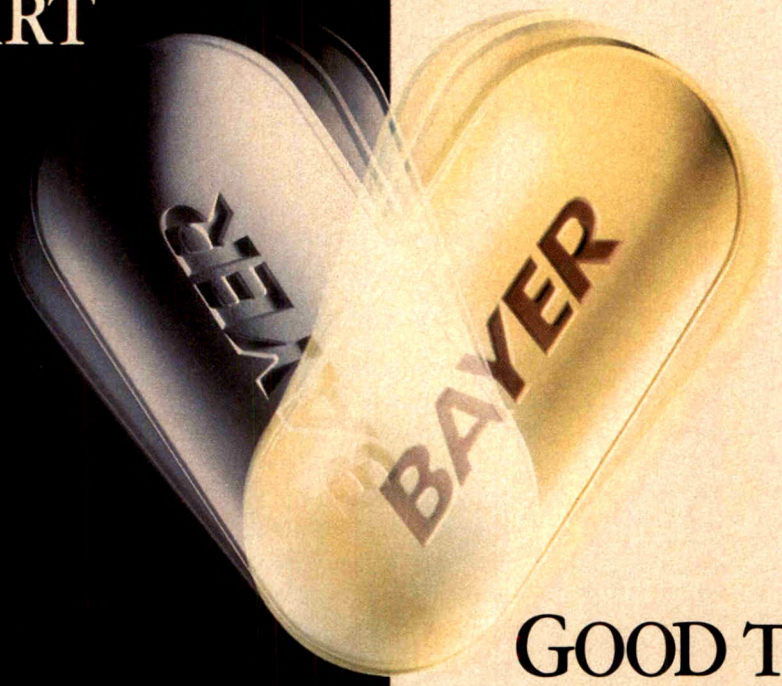
Maggie Riley-Hagan, Ronald M. Peshock, James Stray-Gundersen, Jose Katz, Timothy W. Ryschon, and Jere H. Mitchell

Magnetic resonance imaging, a 3-dimensional technique, was used to examine left ventricular (LV) mass, LV end-diastolic volume and mean wall thickness. Three groups of female endurance athletes were compared with sedentary controls, matched for height and body weight. The percent body fat mean and maximal oxygen uptake were similar ($p > 0.05$) among all athletic groups, but significantly different from the control group. LV mass, LV end-diastolic volume and mean wall thickness were also similar among the athletic groups and significantly larger than control values: LV mass, LV end-diastolic volume and mean wall thickness. The LV mass/LV end-diastolic volume ratio was similar ($p > 0.05$) among all groups. Our findings indicate that LV mass, LV end-diastolic volume and mean wall thickness are greater in endurance athletes than in sedentary controls and that the increase in LV mass is proportional to the increase in LV end-diastolic volume.

Continued on page A39

OR PROPHYLAXIS POST-MI AND IN UNSTABLE ANGINA

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BRIEF SUMMARY

Therapy BAYER® ENTERIC Aspirin
Delayed-Release Enteric Aspirin (Acetylsalicylic Acid) Caplets to Help Reduce the Risk of Second MI or MI in Unstable Angina

DOSAGE AND ADMINISTRATION:
Although most of the studies used dosages exceeding 300 mg, two trials used only 300 mg daily, and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 mg or a conventional 325 mg aspirin dose daily is a reasonable routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

CARDIOVASCULAR AND BIOCHEMICAL:
In the AMIS trial, the dosage of 1,000 mg per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 mm) and diastolic BP (0.5 to 0.6 mm), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased but by less than 1.0 mg percent. Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 mg per day, be seen at regular intervals to assess changes in these measurements.

BIOAVAILABILITY:
A single-dose bioavailability study[1] has demonstrated that plasma acetylsalicylic acid and salicylic acid concentrations resulting from Therapy BAYER® ENTERIC are equivalent to those from plain aspirin, i.e., non-enteric-coated aspirin. As expected, the enteric coating on Therapy BAYER® ENTERIC results in delayed absorption (peak achieved at approximately five hours postdosing) relative to plain aspirin. Dissolution of the enteric coating occurs at neutral-to-basic pH and is therefore dependent on gastric emptying into the duodenum. With continued dosing, appropriate therapeutic plasma levels are maintained.

SAFETY:
The safety of enteric-coated aspirin has been demonstrated in a number of endoscopic studies comparing enteric-coated aspirin and plain aspirin, as well as plain buffered and "arthritis strength" preparations. In these studies, endoscopies were performed in healthy volunteers before and after either two-day or 14-day administration of aspirin doses of 3,900 or 4,000 mg per day. Compared to all the other preparations, the enteric-coated aspirin produced significantly less damage to the gastric mucosa. There was also statistically less duodenal damage when compared with the plain, i.e., non-enteric-coated, aspirin.

ADVERSE REACTIONS:
Gastrointestinal reactions: Doses of 1,000 mg per day of aspirin caused gastrointestinal symptoms and bleeding that, in some cases, were clinically significant. In the largest postinfarction study (the Aspirin Myocardial Infarction Study [AMIS] with 4,500 people),[2] the percentage of incidences of gastrointestinal symptoms for the aspirin (1,000 mg of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were stomach pain (14.5%, 4.4%), heartburn (11.9%, 4.8%), nausea and/or vomiting (7.6%, 2.1%), and hospitalization for GI disorder (4.9%, 3.5%). In the AMIS and other trials, aspirin-treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable angina with buffered aspirin in solution.

PROFESSIONAL WARNING:
Occasional reports have documented individuals with impaired gastric emptying in whom there may be retention of one or more enteric-coated aspirin caplets over time. This phenomenon may occur as a result of outlet obstruction from ulcer disease alone or combined with hypotonic gastric peristalsis. Because of the integrity of the enteric coating in an acidic environment, these caplets may accumulate and form a bezoar in the stomach. Individuals with this condition may present with complaints of early satiety or of vague upper abdominal distress. Diagnosis may be made by endoscopy or by abdominal films, which show opacities suggestive of a mass of small caplets.[3] Management may vary according to the condition of the patient. Options include gastrotomy and alternating slightly basic and neutral lavage.[4] While there have been no clinical reports, it has been suggested that such individuals may also be treated with parenteral cimetidine (to reduce acid secretion) and then given sips of slightly basic liquids to effect gradual dissolution of the enteric coating. Progress may be followed with plasma salicylate levels or via recognition of tinnitus by the patient.

It should be kept in mind that individuals with a history of partial or complete gastrectomy may produce reduced amounts of acid and therefore have less acidic gastric pH. Under these circumstances, the benefits offered by the acid-resistant enteric coating may not exist.

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1075
Diagnosis and Management (by Subxiphoid Pericardiotomy) of Large Pericardial Effusions Causing Cardiac Tamponade
Thomas C. Wall, Paul T. Campbell, Christopher M. O'Connor, Peter Van Trigt, Richard T. Kenney, Khalid H. Sheikh, Joseph A. Kisslo, and G. Ralph Corey

To determine the clinical features, course and outcome of patients with cardiac tamponade, 57 consecutive patients with new, large pericardial effusions were studied. This care series disclosed several unexpected findings. First, cardiac tamponade occurred in almost 50% of patients with new, large effusions. Second, collagen-vascular disease appeared to be a more frequent cause of tamponade than previous studies suggested. Third, clinical evaluation resulted in few idiopathic etiologies. Finally, subxiphoid pericardiotomy was an effective procedure for diagnosis and therapy of patients with large pericardial effusions.

METHODS

1079
Comparison of Single and Biplane Ventriculography for Determination of Left Ventricular Volume and Ejection Fraction
Walter C. Brogan, III, D. Brent Glamann, Richard A. Lange, and L. David Hillis

This study was done to compare single and biplane left ventriculography in quantitating left ventricular volumes and ejection fraction. The analysis was performed using ventriculograms from 152 patients, 102 of whom had segmental hypokinesia, akinesia or dyskinesia and 46 a depressed ejection fraction. There was excellent agreement between single and biplane ventriculography in measuring left ventricular end-diastolic volume, end-systolic volume and ejection fraction, even in patients with depressed ejection fraction and segmental wall motion abnormalities.

BRIEF REPORTS

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Marked Benefit with Sustained-Release Niacin Therapy in Patients with "Isolated" Very Low Levels of High-Density Lipoprotein Cholesterol and Coronary Artery Disease
Carl J. Lavie, Lois Mailander, and Richard V. Milani

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Effect of Restenosis After an Earlier Angioplasty at Another Coronary Site on the Frequency of Restenosis After a Subsequent Coronary Angioplasty
Peter B. Berger, Malcolm R. Bell, David R. Holmes, Jr., LaVon Hammes, Jon L. Kosanke, and Stuart J. Bresee

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Effect of Activity on Circadian Variation in Time of Onset of Acute Myocardial Infarction
John Zornosa, Martha Smith, and William Little

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Bronchocoronary Collateral Circulation in Patients with Three-Vessel Coronary Artery Disease and Normal Left Ventricular Function
Simon Weber, Gérard Pasquier, Yves Martin-Bouyer, Marc Riquet, Philippe D'Athis, Lisa Naditch, and François Guerin

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Persistent Inappropriate Sinus Tachycardia After Radiofrequency Current Catheter Modification of the Atrioventricular Node
Frederick A. Ehlert, Jeffrey J. Goldberger, Rodney Brooks, Scott Miller, and Alan H. Kadish

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Determinants of Impedance During Radiofrequency Catheter Ablation in Humans
Mark Borganelli, Rafel El-Atassi, Angel Leon, Steven J. Kalbfleisch, Hugh Calkins, Fred Morady, and Jonathan J. Langberg

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Detection of Atrial Tachyarrhythmias by Transesophageal Pacing and Recording at Rest and During Exercise in Children with Ventricular Preexcitation
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Mono- Versus Double-Balloon Technique for Commissural Splitting After Percutaneous Mitral Valvotomy
Antonio Fernández-Ortiz, Carlos Macaya, Fernando Alfonso, Rosana Hernández, Andrés Iñiguez, Javier Goicolea, Camino Bañuelos, and Pedro Zarco

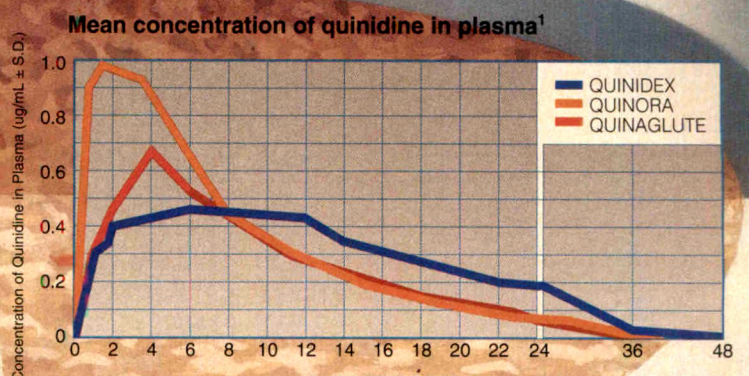
1102
Role of Transesophageal Echocardiography in Diagnosis of Subaortic Aneurysm
John Skoularigis, Ehud Deviri, Thomas Wisenbaugh, Rafique Essop, Shirley Middlemost, and Pinhas Sareli

1104
Menopause-Induced Changes in Doppler-Derived Parameters of Aortic Flow in Healthy Women
Amos Pines, Enrique Z. Fisman, Yaacov Drory, Yoram Levo, Joseph Shemesh, Efraim Ben-Ari, and Daniel Ayalon

Continued on page A43

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See brief summary of prescribing information on adjacent page.

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The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncracy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

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1. Wright GJ. Relative bioavailability and dosage form performance from single doses of quinidine as Quinidex Extentabs®, Quinaglute® Dura-Tabs®, and Quinora® in healthy male volunteers. Data on file, A.H. Robins Co., 1981.
2. Morganroth J, Hunter H. Comparative efficacy and safety of short-acting and sustained release quinidine in the treatment of patients with ventricular arrhythmias. *Am Heart J.* 1985;110:1176-1181.
3. IMS National Prescription Audit, May 1991.

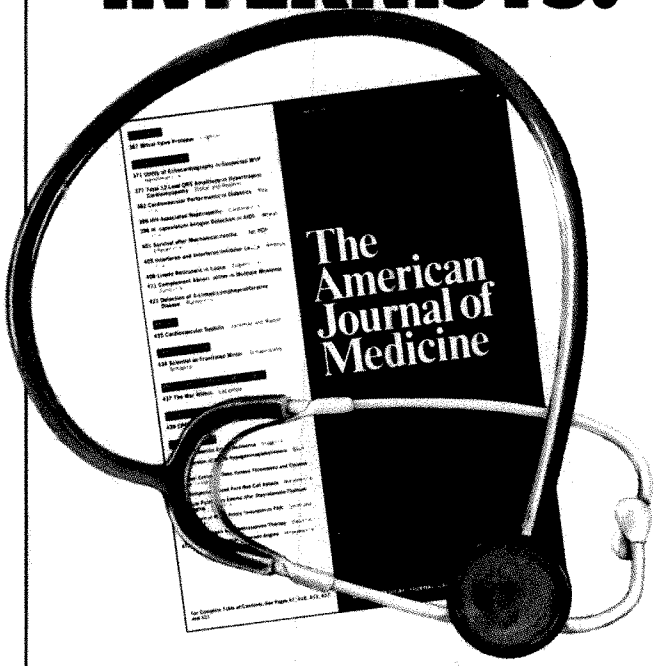
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Use of Intracoronary Ultrasound to Identify the "True" Coronary Lumen in Chronic Coronary Dissection Treated with Intracoronary Stenting
Thomas E. Schryver, Jeffrey J. Popma, Kenneth M. Kent, Martin B. Leon, Sharon Eldredge, and Gary S. Mintz

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Ocular Deformation After Long-Term Repeated Bulbar Compression for Termination of Paroxysmal Tachycardia
Per I. Hoff, Svein Faerestrand, Ole-Jörgen Ohm

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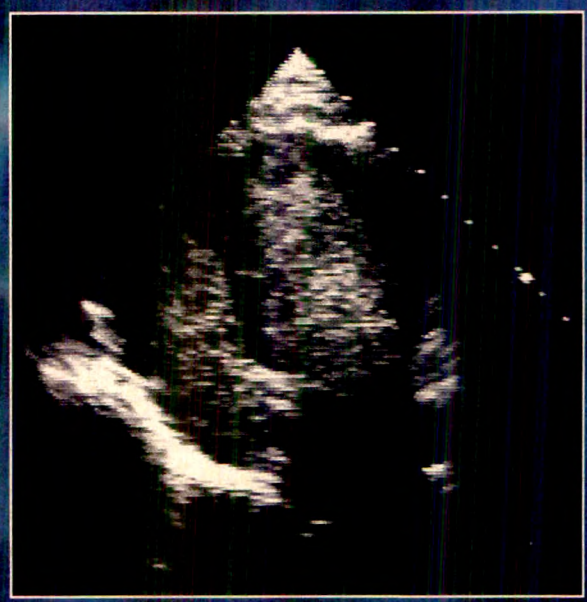
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Calculation of Valve Area by the Gorlin Formula and Continuity Equation
Dawod Sharif and Edward G. Abinader

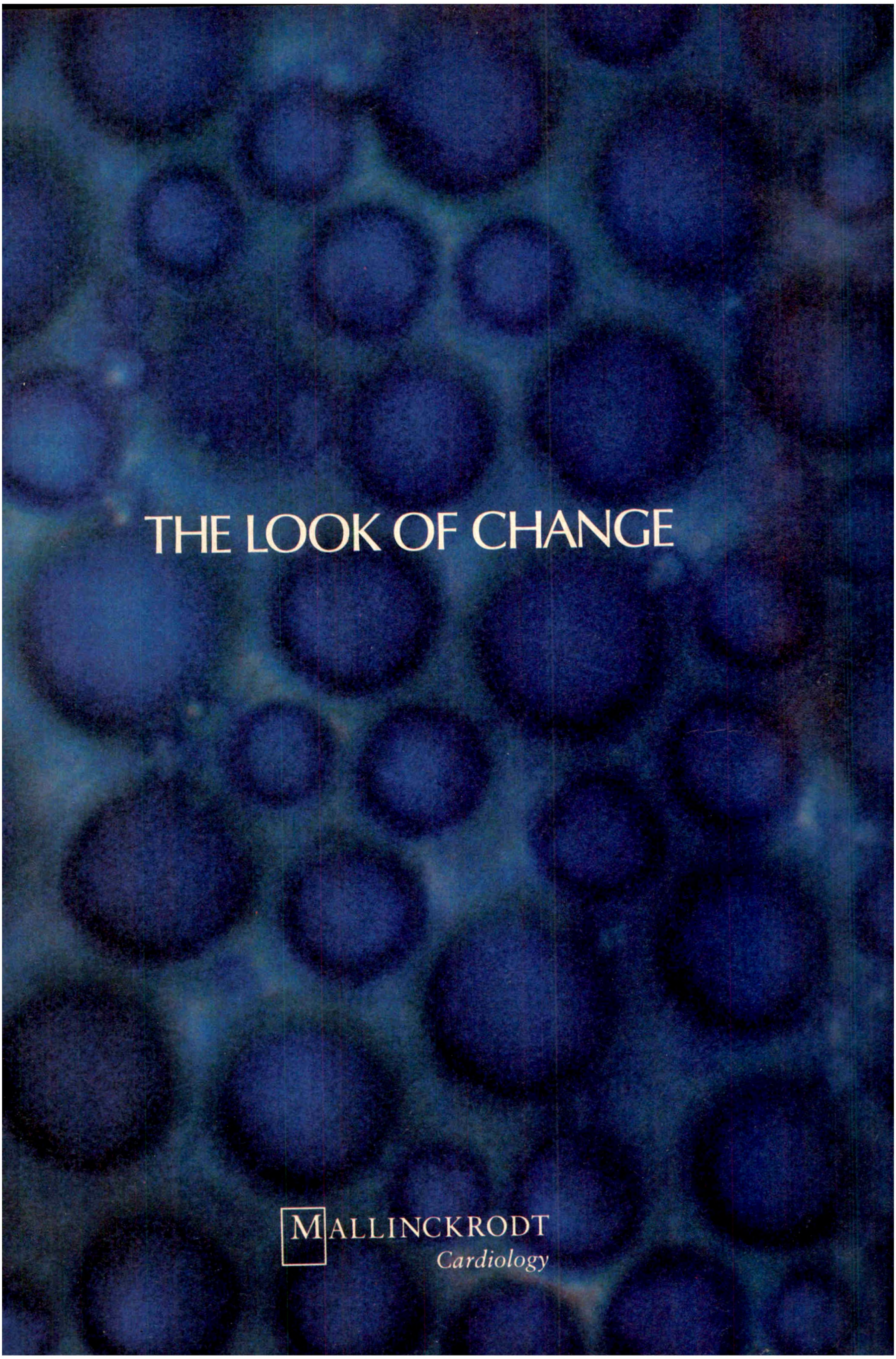
Percutaneous Pulmonary Balloon Valvuloplasty in Adults
Wing-Hing Chow and Tsun-Cheung Chow

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Correction

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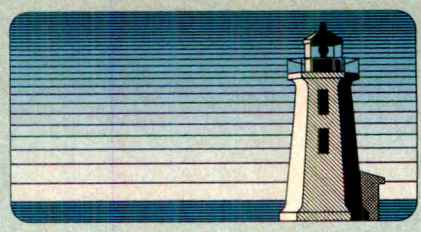

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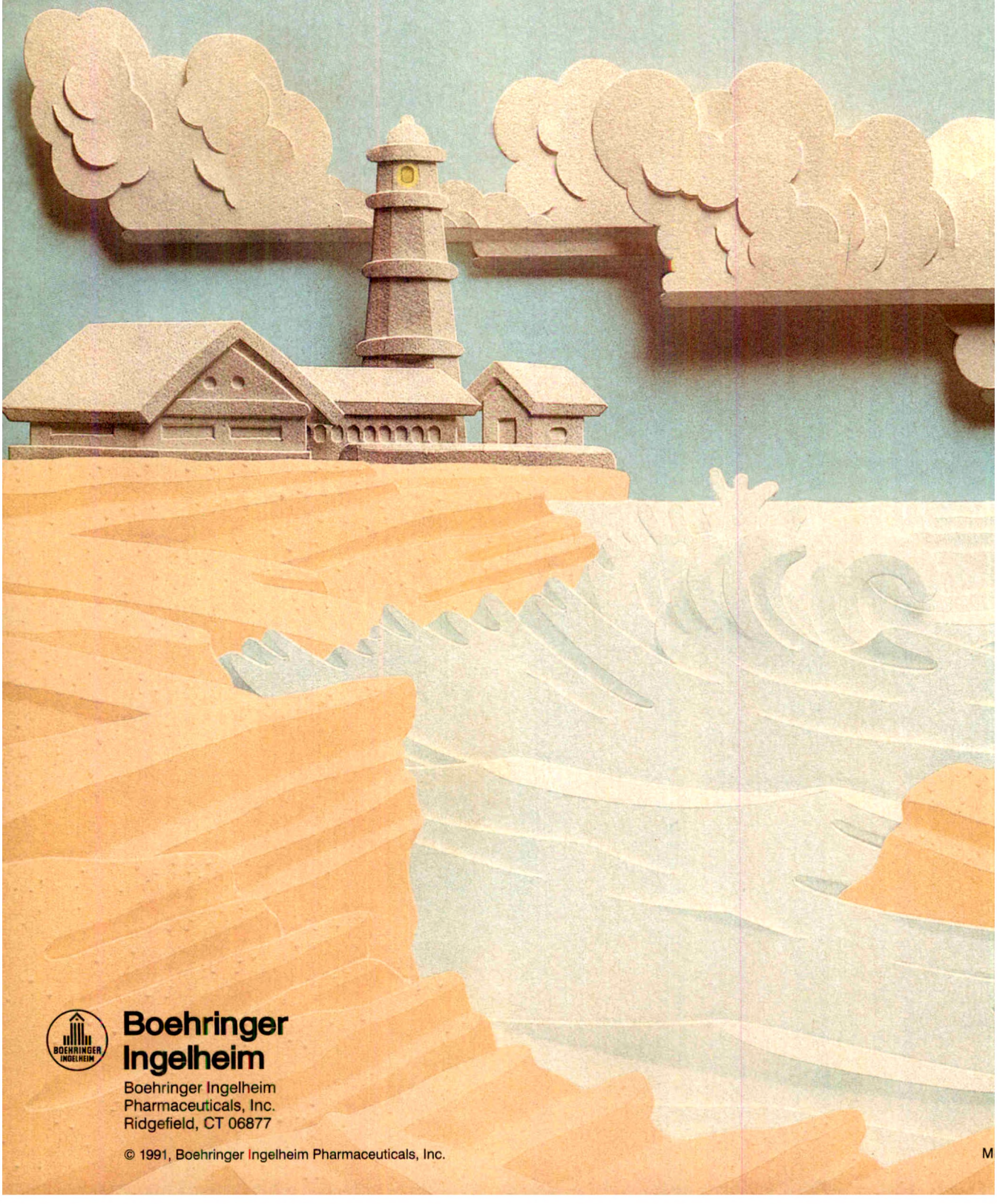
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The American Journal of Cardiology

APRIL 15, 1992, VOL. 69, NO. 12

Interrelation of Left Ventricular Ejection Fraction, Pulmonary Congestion and Outcome in Acute Myocardial Infarction

Shmuel Gottlieb, MD, Arthur J. Moss, MD, Michael McDermott, PhD, and Shirley Eberly, MS

The interrelation of different grades of pulmonary congestion evaluated by chest roentgenogram in the coronary care unit, predischarge left ventricular (LV) ejection fraction (EF) and long-term prognosis was studied in 1,850 surviving patients of acute myocardial infarction (AMI). Pulmonary congestion was categorized as: none, mild or moderate, or severe; LVEF was classified as: ≥40%, 25 to 39%, or <25%. The majority of patients (1,060; 57%) had an LVEF ≥40% and no signs of pulmonary congestion. Severe pulmonary congestion was noted in 63 patients (3.4%), 17 with LVEF <25% and 16 with LVEF ≥40%. One hundred twenty-five patients (6.8%) had an LVEF <25%, 49 of whom had no signs of pulmonary congestion. During a mean 2-year follow-up, cardiac mortality occurred in 212 patients (11.5%). The cardiac mortality rate was related to both predischarge LVEF impairment and severity of pulmonary congestion. Cardiac mortality hazard ratios (95% confidence intervals [CI]) for LVEF <25%, and 25 to 39% were 5.32 (CI 3.49, 8.13; p <0.0001) and 2.91 (CI 2.10, 4.02; p <0.0001), respectively, where a referent hazard ratio of 1 was assigned to patients with LVEF ≥40% and to those with no pulmonary congestion. Development of pulmonary congestion during AMI significantly increased the cardiac mortality risk derived from LVEF, with a marked mortality effect in patients with severe pulmonary congestion; (hazard ratio 4.20; 95% CI 2.67, 6.62; p <0.0001). These findings emphasize the independent prognostic role of pulmonary congestion and highlight the interactive mechanisms (systolic and diastolic dysfunctions) responsible for unfavorable outcome in surviving AMI patients.

(Am J Cardiol 1992;69:977–984)

From the Heart Research Follow-Up Program and the Division of Biostatistics, University of Rochester School of Medicine and Dentistry, Rochester, New York. Dr. Gottlieb was the recipient of a fellowship grant from the American Physicians Fellowship Inc., Boston, Massachusetts. Manuscript received July 24, 1991; revised manuscript received and accepted December 13, 1991.

Address for reprints: Shmuel Gottlieb, MD, P.O. Box 492, the Heiden Department of Cardiology, Bikur Cholim Hospital, Jerusalem, Israel 91000.

Previous studies showed that left ventricular (LV) function is the major determinant of outcome in patients who survived an acute myocardial infarction (AMI)[1–3] and that cardiac mortality during the first year after AMI increases progressively as LV ejection fraction (EF) decreases to <40%.[1,2] Other studies showed that in patients recovering from AMI, pulmonary congestion during hospitalization is an important independent predictor of short-[4–7] and long-term[1,3,6–11] prognoses. A few studies reported on the interrelation between pulmonary congestion during the acute phase of AMI and predischarge LVEF, and their prognostic significance,[10,11] including patients with pulmonary edema and good LV function.[12] However, the interrelation and prognostic significance of these 2 different LV dysfunction parameters have not been evaluated in a large, well-defined patient population and have not been examined at different grades of pulmonary congestion and LVEF. This study assesses the interrelation of different grades of pulmonary congestion evaluated by chest roentgenogram in the coronary care unit, predischarge radionuclide LVEF, and the prognostic significance in a large number of surviving AMI patients. The study involves a retrospective analysis of data from 2 prospective multicenter populations obtained from university and community hospitals, with a broad geographic representation.

METHODS

Study population: The study population comprised 1,850 surviving AMI patients; 790 were from the Multicenter Post-Infarction Program (MPIP; n = 867),[1] and 1,060 were placebo-assigned patients from the Multicenter Diltiazem Post-Infarction Trial (MDPIT; n = 1,234)[13] who had undergone both chest roentgenogram in the coronary care unit and predischarge LVEF. The original MPIP patients were enrolled between January 1, 1979 and December 31, 1980, whereas the MDPIT patients were enrolled between February 17, 1983 and June 30, 1986. Average follow-up duration was approximately 2 years in both studies. Only 86 patients (4.6%) received thrombolytic therapy. A detailed description of the design, organization, patient recruitment, data acquisition, data management and follow-up of these 2 studies was previously reported.[1,13]

Left ventricular function variables: Two variables measuring LV function were included in this study. The

TABLE I Population Characteristics

	Combined (n = 1850)	MPIP (n = 790)	MDPIT (n = 1060)	p Value*
Years of study	1979–1987	1979–1981	1983–1987	
Mean age (yr)	58 ± 10	57 ± 9	58 ± 10	
Age ≥ 60	877 (47%)	344 (43%)	553 (50%)	0.004
Men/women (% men)	1,451/399 (78%)	617/173 (78%)	834/226 (79%)	
Treatment for hypertension	692 (37%)	294 (37%)	398 (38%)	
History of myocardial infarction	404 (22%)	183 (23%)	221 (21%)	
New York Heart Association†	480 (26%)	294 (37%)	186 (18%)	<0.0001
Blood urea nitrogen > 35 mg%	141 (8%)	60 (8%)	81 (8%)	
> bibasilar pulmonary rales	189 (10%)	113 (14%)	76 (7%)	<0.0001
Pulmonary congestion‡				
None	1,399 (76%)	568 (72%)	831 (79%)	
Mild	310 (17%)	146 (18%)	164 (15%)	<0.002§
Moderate	78 (4%)	37 (5%)	41 (4%)	
Severe	63 (3%)	39 (5%)	24 (2%)	
Radionuclide ejection fraction				
Mean	46 ± 14	46 ± 15	47 ± 14	
≥ 40%	1,266 (68%)	524 (66%)	742 (70%)	
25–39%	459 (25%)	216 (27%)	243 (23%)	0.09‖
<25%	125 (7%)	50 (6%)	75 (7%)	
Ventricular ectopic beats ≥ 10/hr	306 (18%)	147 (20%)	159 (17%)	
β blockers at discharge	821 (44%)	256 (32%)	565 (53%)	<0.0001
Average follow-up (mos)	24	22	25	
Event rates				
1-year cardiac mortality rate	129 (7%)	58 (7%)	71 (7%)	
Cardiac mortality rate	212 (11%)	107 (14%)	105 (10%)	0.015
Total mortality rate	275 (15%)	131 (17%)	144 (14%)	0.07

*MPIP vs MDPIT.
†New York Heart Association functional classification 1 month before entry.
‡Confirmed by chest roentgenogram.
§Among 4 grades of pulmonary congestion; ‖among 3 levels of left ventricular ejection fraction.
MDPIT = Multicenter Diltiazem Post-Infarction Trial (placebo arm); MPIP = Multicenter Post-Infarction Research Group.

definitions of these variables were predetermined and specified in a manual of operations, and were the same in both MPIP and MDPIT.

1. Radionuclide LVEF was obtained 5 to 25 days (mean 13 ± 7 [MPIP] and 8 ± 4 [MDPIT]) after the index AMI at the respective enrolling institutions using either gated (MUGA) or first-pass techniques. Core laboratory analysis was not performed. A 3-level variable was used for LVEF: ≥40%, 25 to 39% or <25%. The cutoff point of LVEF <40% was chosen on the basis of previous studies.[1,2,13]

2. The most severe pulmonary congestion on chest roentgenograms obtained in the coronary care unit were interpreted by staff radiologists at each participating hospital and coded on the official written report according to a 4-grade severity scale: none, mild (venous congestion), moderate (interstitial congestion) or severe (pulmonary edema). Core laboratory analysis was not performed.

Therapy and end point: Therapy was not controlled and was managed by the patient's personal physician. The end point of interest in this study was cardiac mortality during a mean follow-up of 24 months. A 4-member mortality subcommittee (the same physicians for MPIP and MDPIT) reviewed independently the information on the causes and circumstances surrounding each death occurring on or before December 31, 1981 for MPIP, and June 30, 1987 for MDPIT. Data regarding each death was obtained by the study coordinators from relatives, witnesses, death certificates, attending physicians, hospital records and autopsy reports. Each mortality event was categorized as either cardiac or noncardiac according to written criteria.

Statistical methods: The baseline characteristics of MPIP and MDPIT patients included in the study were compared using (where appropriate) either a chi-square or 2-sample *t* test. Results of continuous variables are reported as mean ± 1 SD. A 2-sided p value <0.05 was considered statistically significant.

The primary analyses were performed using the Cox proportional hazards regression model[14] (BMDP-2L computer program)[15]; the participating hospitals were entered as stratification factors, and variables representing various grades of pulmonary congestion and LVEF were included in the model as main effects. A 3-grade variable was used for pulmonary congestion (none, mild or moderate, or severe) and for LVEF (≥40%, 25 to 39% or <25%). Comparisons of patients with a particular grade of either pulmonary congestion or LVEF to the corresponding referent category are re-

ported in terms of the hazard ratio. The referent groups were chosen to be patients with no pulmonary congestion and those with LVEF ≥40% (hazard ratio 1). A test for interaction between pulmonary congestion and LVEF for cardiac mortality was also performed. The aforementioned Cox model was fitted both with and without β blockers as a main effect, where β-blocker use was determined at the time of discharge from the hospital.

Because the data are a composite of 2 different studies (MPIP and MDPIT), and because in general MPIP patients had more severe cardiac disease than did MDPIT ones, we checked whether the results were consistent across both studies, and whether the study itself did not independently contribute to the risk of a patient. A dichotomized "study" variable indicating whether the patient participated in the MPIP study was included as a main effect in the Cox model, together with main effect terms for pulmonary congestion and LVEF. Terms of interaction between these variables and the "study" variable were also included in the Cox model, and were tested for their significance. Another approach to answering this question was by fitting the Cox model separately for the MPIP and MDPIT studies.

Cumulative cardiac mortality rates over time were described using the method of Kaplan and Meier,[16] and differences between the mortality curves were assessed by the log-rank test[17] using the BMDP-1L computer program.[18] For each of the 3 levels of LVEF, a set of 3 curves was constructed according to the 3 grades of pulmonary congestion. The reported analyses involved the analytic data bases released February 14, 1985 for MPIP, and April 16, 1988 for MDPIT.

RESULTS

Comparability of study populations: The baseline characteristics and outcome events of the combined study population (n = 1,850), and separately for MPIP (n = 790) and MDPIT (n = 1,060) are presented in Table I. The 2 populations were similar in terms of history of hypertension, blood urea nitrogen >35 mg%, LVEF and frequency of ventricular ectopic beats on Holter recording. The patients in MPIP had more severe cardiac disease than did those in MDPIT, as evidenced by the higher NYHA class and greater prevalence of pulmonary congestion. Beta-blocker use at discharge from the hospital was higher in MDPIT than MPIP patients. The frequency of AMI type and location could not be compared, because the 2 studies used different electrocardiographic coding procedures (Minnesota code[19] in MPIP, and Manhattan code[20] in MDPIT).

Relation between pulmonary congestion and left ventricular ejection fraction: The frequency distribution and the relation between pulmonary congestion on chest roentgenogram during the coronary care unit phase and predischarge LVEF among 1,850 patients who survived AMI are shown in Figure 1 and Table II. Most patients (1,060; 57%) had an LVEF ≥40% and no pulmonary congestion. However, only 17 patients (1%) had an LVEF <25% and severe pulmonary congestion. In general, the more severe the pulmonary congestion grade, the lower the LVEF (Figure 1) (F = 69.98, p <0.001 [analysis of variance]). However, a considerable discrepancy between pulmonary congestion and LVEF exists, with an overlap in the LVEF values for all grades of pulmonary congestion. Noteworthy are the 16 and 31 patients who demonstrated severe and moderate pulmonary congestion, respectively, during the acute phase of AMI, but had a predischarge LVEF ≥40%, and furthermore, the 49 patients with LVEF <25% who had no pulmonary congestion.

TABLE II Frequency Distribution and Cardiac Mortality Rates by Pulmonary Congestion and Left Ventricular Ejection Fraction

Pulmonary Congestion	Left Ventricular Ejection Fraction			
	≥40%	25–39%	<25%	Total
None	55/1,060 (5.2%)	47/290 (16.2%)	14/49 (28.6%)	116/1,399 (8.3%)
Mild	16/159 (10.0%)	19/112 (17.0%)	12/39 (30.8%)	47/310 (15.2%)
Moderate	4/31 (12.9%)	7/27 (25.9%)	8/20 (40%)	19/78 (24.4%)
Severe	7/16 (43.8%)	15/30 (50%)	8/17 (47.1%)	30/63 (47.6%)
Total	82/1,266 (6.5%)	88/459 (19.2%)	42/125 (33.6%)	212/1,850 (11.5%)

Numerator is number of cardiac deaths during follow-up, denominator is number of patients, and cardiac mortality rate is in parentheses.

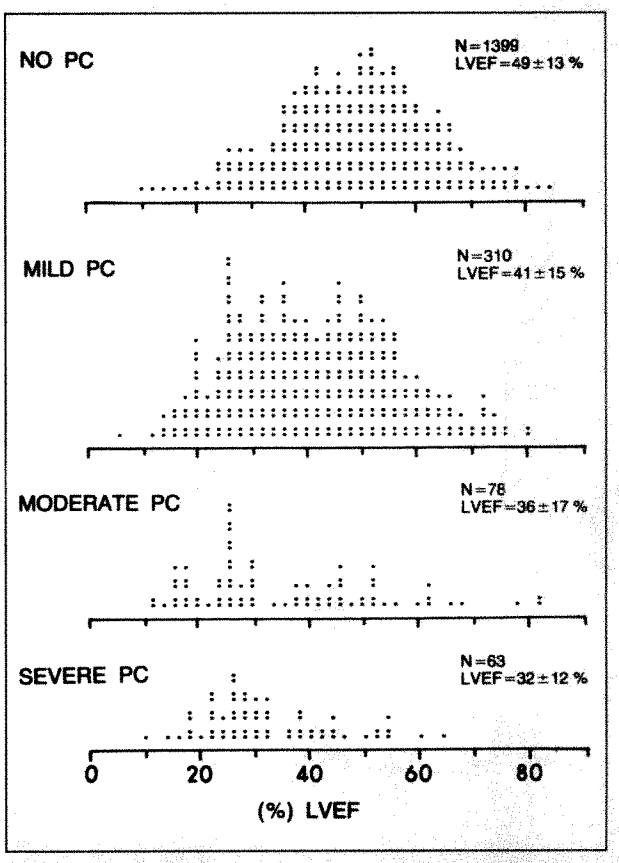


FIGURE 1. Distribution of predischarge left ventricular ejection fraction (LVEF) by 4 grades of chest roentgenographic pulmonary congestion (PC). In patients with no pulmonary congestion, each *dot* represents 6 cases, and in the other categories, 1 case. Mean ± 1 SD of left ventricular ejection fraction is reported in each group.

Cardiac mortality: During follow-up, cardiac mortality occurred in 212 patients (11.5%), and almost half of the mortality events (46%) occurred during the first 6 months after AMI. The cardiac mortality rate was related to both degree of LVEF impairment and severity of pulmonary congestion (Table II and Figure 2, A and B); the lower the LVEF, the higher the cardiac mortality rate, with a progressive increase in mortality as the LVEF decreased to <40% (Figure 2A). A progressive increase in cardiac mortality rate was also related to increasing severity of pulmonary congestion (Figure 2B and Table II). Noteworthy is the similar graded increase in cardiac mortality rate as a function of pulmonary congestion severity or LVEF impairment. The cardiac mortality rate in the different subgroups categorized by both LVEF and pulmonary congestion is shown in Table II and Figure 3. At each level of LVEF, increasing severity of pulmonary congestion progressively augmented the cardiac mortality rate, with a marked effect in patients with severe pulmonary congestion. The lowest cardiac mortality rate was observed in patients with LVEF ≥40% without any signs of pulmonary congestion (5.2%). The highest mortality rate (44 to 50%) was observed in patients with severe pulmonary congestion, where the level of LVEF had only a small influence on cardiac mortality, possibly owing to the small number of patients (n = 17) with severe pulmonary congestion and LVEF <25% who survived AMI and were discharged from the hospital.

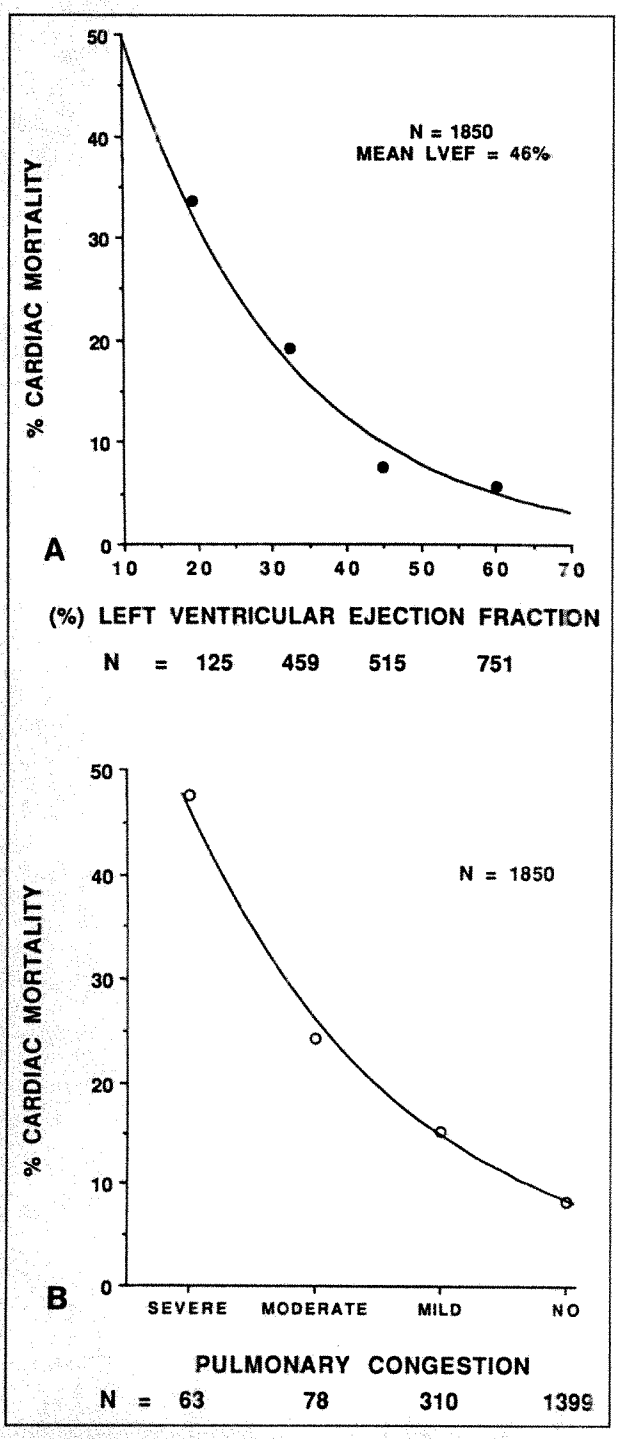


FIGURE 2. Cardiac mortality rate at 4 levels of predischarge left ventricular ejection fraction (LVEF) (<25%, 25 to 39%, 40 to 50% and >50%) *(A)* and at 4 grades of pulmonary congestion (no, mild, moderate and severe) *(B)*. Correlation coefficients for best fitted curves for left ventricular ejection fraction and pulmonary congestion were: r = 0.975 (p <0.0001) and 0.998 (p <0.0001), respectively.

Survival analyses: In the survival analyses, the main effects of pulmonary congestion and LVEF were included in a Cox model, using 3 impairment levels for LVEF (≥40%, 25 to 39% and <25%), and 3 severity gradations for pulmonary congestion (none, mild or moderate, and severe). A gradation in hazard ratio was found as pulmonary congestion or LVEF impairment increased (Table III). For example, the hazard ratio for a patient with severe pulmonary congestion and an LVEF of 25 to 40% was 12.22 (2.91 × 4.20), relative to one with an LVEF ≥40% and no pulmonary congestion. Inclusion of β-blocker use (a noncontrolled study medication) at discharge from the hospital in this model did not significantly change the hazard ratios for pulmonary congestion and LVEF. Beta blockers had a beneficial effect and decreased the hazard ratio by a factor of

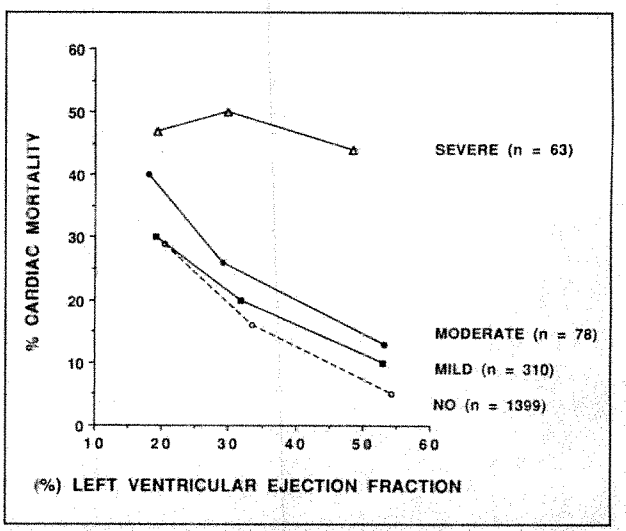


FIGURE 3. Cardiac mortality rate at 3 levels of predischarge left ventricular ejection fraction (<25%, 25 to 39% and ≥40%) and at 4 grades of pulmonary congestion (no, mild, moderate and severe). Each *point* represents mortality rate and mean left ventricular ejection fraction in that combined category.

0.7 (95% confidence interval 0.50, 0.99; p <0.04) at the various grades of pulmonary congestion and LVEF.

There was a borderline but not significant (p = 0.07) interaction between pulmonary congestion and LVEF in the Cox model. This borderline interaction is also suggested by Figure 3, showing parallel trends for none, mild and moderate grades of pulmonary congestion at all levels of LVEF, but a departure from this trend for those with severe pulmonary congestion. The Cox model for this interaction revealed a similar trend in pulmonary congestion and LVEF hazard ratios, as with the model without interaction, with a marked effect in patients with severe pulmonary congestion.

The inclusion of the "study" variable (MPIP vs MDPIT) in the Cox model (either as a main effect or interaction term with pulmonary congestion and LVEF) did not significantly alter the models (p <0.4). Furthermore, separate Cox models for both MPIP and MDPIT revealed similar cardiac mortality hazard ratios to that of the combined population. This supports our assumption that the effects of pulmonary congestion and LVEF on cardiac mortality are consistent across both studies and provides justification for combining the data.

TABLE III Cardiac Mortality Hazard Ratios (Cox model) for Pulmonary Congestion and Left Ventricular Ejection Fraction

Predictor Variable	Hazard Ratio	95% CI	p Value
Pulmonary congestion			
None	1.00		
Mild or moderate	1.43	(1.02, 2.00)	<0.04
Severe	4.20	(2.67, 6.62)	<0.0001
Ejection fraction			
≥40%	1.00		
25–39%	2.91	(2.10, 4.02)	<0.0001
<25%	5.32	(3.49, 8.13)	<0.0001

CI = confidence interval.

The Kaplan-Meier cumulative cardiac mortality curves for the 3 pulmonary congestion grades (none, mild or moderate, and severe) at each of the 3 grades of LVEF (≥40%, 25 to 39% and <25%) are shown in Figure 4. A significant effect (p <0.0001) of the severity of pulmonary congestion on the mortality curves was noted for LVEF of ≥40% and 25 to 39%, mainly owing to the high-risk group with severe pulmonary congestion. The same pattern for the mortality curves was noted in patients with LVEF <25% (mainly in those with severe pulmonary congestion). However, the differences between the mortality curves did not reach statistical significance, perhaps because of the small number of cases in each category of pulmonary congestion. It is also clear from the curves that LVEF has an effect, because

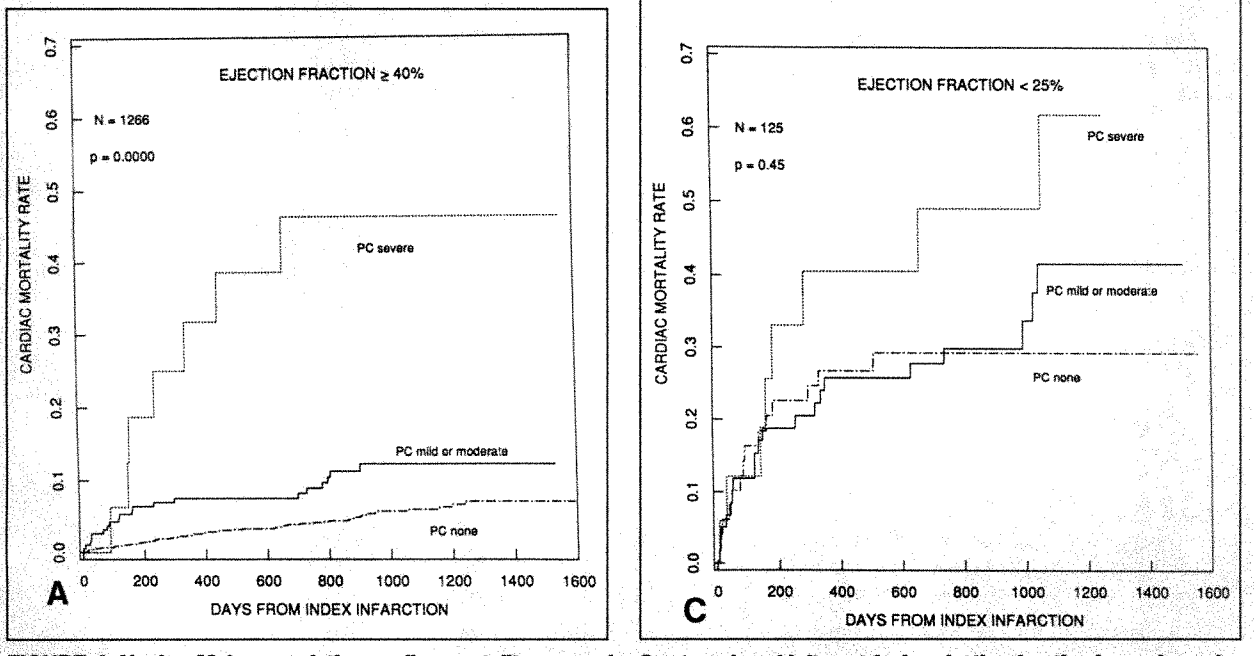


FIGURE 4. Kaplan-Meier cumulative cardiac mortality curves for 3 categories of left ventricular ejection fraction by each grade of pulmonary congestion (PC). A p value indicates significance of difference among 3 curves in each figure. See text for details.

the curves in general are shifted up as LVEF decreases. Most events in patients with very low LVEF (<25%) or with severe pulmonary congestion occurred early during the first 6 months, as can be noted from the steepness of the mortality curve slopes. However, in patients with LVEF ≥40% and without pulmonary congestion, only 25% of the events occurred during the first 6 months after AMI.

DISCUSSION

This study describes a broad aspect of the interrelation and prognostic significance of acute phase pulmonary congestion severity developed in the coronary care unit, and predischarge LVEF impairment in a large, representative population after AMI. Each of these 2 variables measuring LV function was obtained at different phases during AMI and has independent prognostic significance for cardiac mortality during an average 2-year follow-up. The principal finding of this study is that development of pulmonary congestion augments the cardiac mortality risk derived from LVEF at all levels. This finding was more marked in patients with severe pulmonary congestion.

Relation between left ventricular ejection fraction and pulmonary congestion: Most patients (57%) had an LVEF ≥40% and no pulmonary congestion. In the remaining population, patients with more severe pulmonary congestion generally had a lower mean LVEF. However, there was large variability of the LVEF distribution at the different grades of pulmonary congestion (Figure 1). This discrepancy between pulmonary congestion and LVEF is further substantiated by the Cox model that shows that each of these variables is an independent prognostic predictor.

A few previous studies compared the interrelation between pulmonary congestion and LVEF in patients recovering from AMI. These studies also showed a discrepancy between these 2 variables in some subsets of patients.[10-12] Warnowicz et al[12] found similar mortality and rehospitalization rates for ischemic events among 39 patients who developed pulmonary edema during the acute phase of AMI regardless of whether the LVEF was > or <45%. Nicod et al[11] observed that 11% of patients after AMI with LVEF ≥40% had pulmonary congestion, and 19% with LVEF <40% did not. They also noted that the presence of pulmonary congestion increased the 1-year cardiac mortality rate derived from LVEF. Our study (which includes twice the number of patients) confirms these findings for 3 levels of LVEF and for 3 grades of pulmonary congestion (Tables II and III), with further substantiation in patients with low (25 to 39%) and very low (<25%) LVEF.

A progressive increase in cardiac mortality as LVEF decreases to <40% was found in this and previous studies.[1,2] Of interest is the similar graded increase in cardiac mortality rate as a function of the severity of pulmonary congestion (Table II and Figure 2, A and B). Gradation in cardiac mortality associated with pulmonary congestion was observed also by Battler et al[6] in 273 patients.

Diastolic dysfunction: The independent contribution of pulmonary congestion to cardiac mortality can be partially explained by diastolic dysfunction. Transient diastolic dysfunction can have an important role in the development of flash pulmonary edema in patients with ischemic heart disease.[21] However, well-maintained diastolic compliance has been observed in some patients with low LVEF and absence of pulmonary congestion.[22] In some patients, marked pulmonary congestion (more than bibasilar rales) during the acute phase of AMI may represent transient ischemia.[9,10,12] Myocardial ischemia is associated with abnormal ventricular relaxation[23] and impaired distensibility.[24]

Hypertension can cause diastolic dysfunction even in the presence of preserved LVEF[25-27] by increasing systolic stress and afterload, and slowing relaxation, even before development of substantial hypertrophy. Of note, in the current study, history of treated hypertension before the index AMI was observed in 47% of patients with pulmonary congestion compared with 35% without pulmonary congestion. Advanced myocardial hypertrophy is also associated with impaired diastolic relaxation.[28]

Thus, LV dysfunction at the onset of AMI is the sum of contributions from prior AMI, history of hypertension with or without LV hypertrophy, and current irreversible damage and reversible ischemia. Each of these factors participates in creating the clinical presentation during the acute phase of the AMI. Over time, the reversible component can be relieved, and LV dysfunction may become less severe.

Other possible explanations for the discrepancy between pulmonary congestion and preserved LVEF include mitral regurgitation,[29] errors in quantitation of LVEF[30] or in interpretation of chest roentgenogram, and noncardiac causes of pulmonary edema.[31] We have no data to evaluate the frequency of occurrence of these possible causes.

Multivariate survivorship analyses: The aim of this study was to explore the interrelation and prognostic significance of pulmonary congestion during the acute phase of AMI and predischarge LVEF in a large study population, and not to risk-stratify patients recovering from AMI. Therefore, other pertinent variables were not included in the analysis, and the reported hazard ratios are not adjusted for those variables. The hard end point in the present study was cardiac mortality during a mean 2-year follow-up. Pulmonary congestion and LVEF each made an independent prognostic contribution to the risk of cardiac mortality. The Cox model did not include terms of interaction between pulmonary congestion and LVEF, because the significance of their interaction was borderline ($p = 0.07$). However, a model with interaction was tested, which revealed similar findings, with a marked effect in patients with severe pulmonary congestion.

Of interest is the finding that the use of β blockers at discharge from the hospital had a beneficial effect on cardiac mortality (hazard ratio 0.7) similar to that observed in previous β-blocker trials.[32] Our study was not

a β-blocker trial, and therapy with them was managed by the patient's personal physician; thus, the results should be interpreted with caution.

Study limitations: There are several limitations to this retrospective analysis of the clinical data from 2 designed prospective multicenter studies (MPIP, prognostic study; and MDPIT, placebo arm of drug study) performed at 2 different time periods during the last decade (MPIP, 1979 to 1981; and MDPIT, 1983 to 1987). However, the organizational aspects of the 2 studies, follow-up, cardiac mortality definitions and mortality subcommittees were similar. All participating hospitals in MPIP were part of MDPIT. Although there were some imbalances between the 2 study populations regarding the common clinical baseline variables, the "study" variable (MPIP vs MDPIT) did not have a significant contribution to the Cox model. Furthermore, separate Cox models for MPIP and MDPIT revealed similar hazard ratios for pulmonary congestion and LVEF in both studies, thus confirming the validity of combining the 2 studies in a common analysis.

Therapy with vasodilators, digoxin, diuretics, antianginal or coronary bypass was not included in the analysis, and confounding effects cannot be excluded.

We do not have information on cardiac output or pulmonary capillary wedge pressures during the acute phase of AMI. Echocardiographic evaluation of LV hypertrophy and mass, Doppler mitral valve flow velocity and radionuclide angiographic determination of filling rates that may confirm diastolic dysfunction were not available in this study. Furthermore, data regarding ischemic events during follow-up, or infarct type or location by electrocardiographic coding were not included in the analyses, because they were not similarly determined in the MPIP and MDPIT studies.

Pulmonary congestion and LVEF were interpreted at each of the participating hospitals and not in a core laboratory. It is possible that the discrepancy between pulmonary congestion and LVEF (Figure 1) can be partly explained by the lack of central analysis. However, in the analysis, the participating hospitals were entered as a stratification factor in the Cox model, thus controlling for any center bias.

In the present study, very few patients (4.6%) received thrombolytic therapy. Currently, 20% of AMI patients undergo thrombolytic therapy,[33] and patency of the open infarct-related artery is <75%.[34] However, the findings from the current study should also be applicable in patients who undergo thrombolytic therapy, because acute-phase pulmonary congestion and predischarge LVEF represent transient and cumulative damage, respectively, to the myocardium. Thus, predischarge LVEF should reflect global cardiac function, and the prognostic implication of a low LVEF should still be valid.[35]

Clinical implication: Development of pulmonary congestion in the coronary care unit during the acute phase of AMI significantly increases the cardiac mortality risk derived from predischarge LVEF, with a marked mortality effect in patients with severe pulmonary congestion. Because pulmonary congestion in the presence of preserved LV function may be a good clinical index of diastolic function, with LVEF correlating with systolic performance, these findings fit well with the hypothesis that 2 independent measures of overall cardiac performance obtained at different times during the course of AMI may be more useful and meaningful than 1 index to identify high- and low-risk patients recovering from AMI. These findings highlight the interactive mechanisms (systolic and diastolic dysfunctions) responsible for unfavorable outcome in patients after AMI. Further studies are needed to better understand the diastolic dysfunction mechanism and reversibility in the setting of AMI.

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CARDIZEM® CD

(diltiazem HCl)



ONCE A DAY

NEW FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

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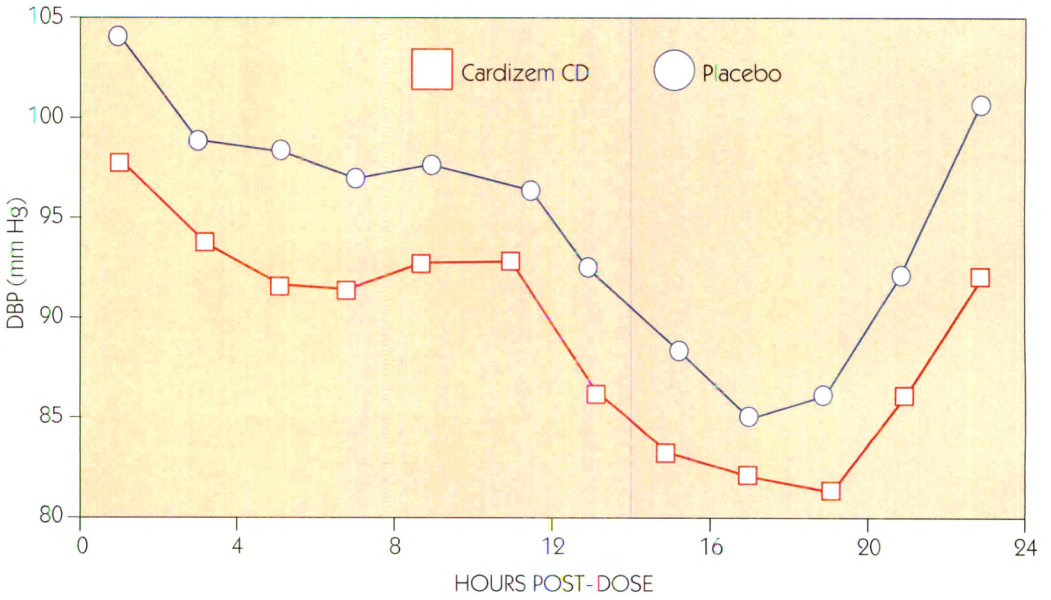
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ONCE A DAY

PROVIDES PROVEN 24-HOUR BLOOD PRESSURE CONTROL WITH A SINGLE DAILY DOSE

A unique delivery system* designed specifically for diltiazem to provide antihypertensive efficacy

Cardizem CD provides clinically significant blood pressure control over a 24-hour period[1]



Study design: placebo-controlled, crossover trial.

Number of patients: 43 mild to moderate hypertensives.

Treatment period: 12 weeks.

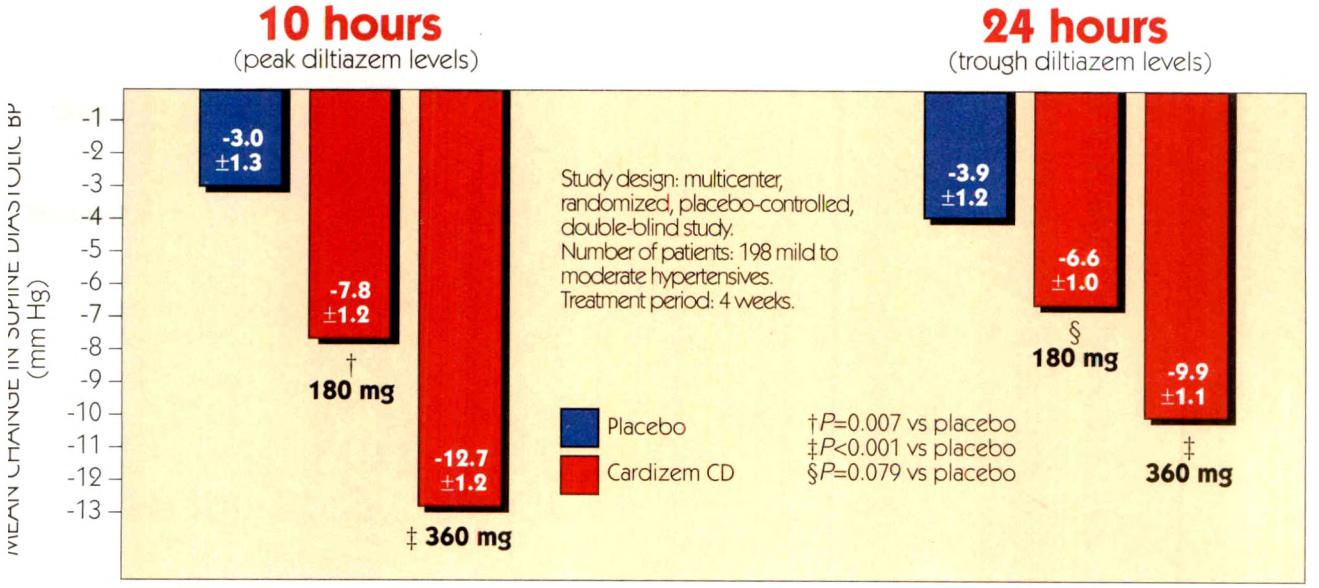
Cardizem CD dosage: 300 mg/day.

* Patent pending.

NEW

PROVEN 24-HOUR EFFICACY

Cardizem CD maintains clinically significant decreases in supine diastolic blood pressure compared to baseline[1]



LOWER PRICE‖

20% lower cost compared to Cardizem® SR (diltiazem HCl) sustained release capsules

NEW

ONCE-A-DAY

CARDIZEM® CD

(diltiazem HCl)

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CARDIZEM® CD

(diltiazem HCl)



EXCELLENT TOLERABILITY

Rarely associated with vasodilatory or GI side effects[1*]

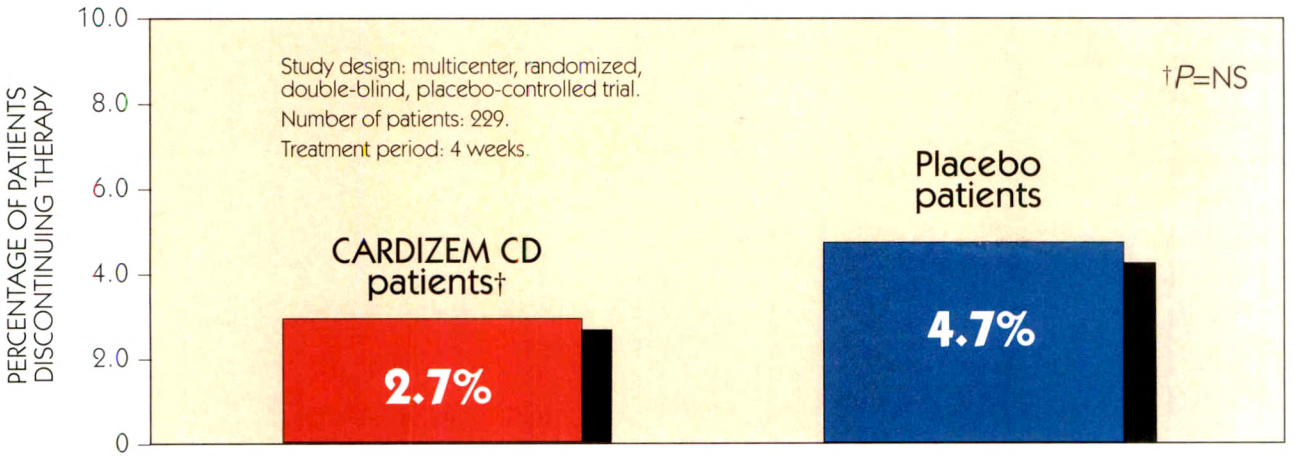
- No reflex tachycardia
- <1% incidence of constipation

Unlike some ACE inhibitors, not associated with cough[1]

* Most commonly reported side effects in placebo-controlled clinical trials include headache, bradycardia, edema, dizziness, ECG abnormality, first-degree AV block, and asthenia.

NEW

A ONCE-A-DAY CALCIUM CHANNEL BLOCKER WITH A DISCONTINUATION RATE COMPARABLE TO PLACEBO



A side-effect profile unlikely to compromise patients with certain concomitant diseases[1-3]

- Including diabetes and coronary artery disease‡

‡ The incidence of hyperglycemia reported with diltiazem has been <1%.

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NEW

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(diltiazem HCl)

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CARDIZEM® CD

(diltiazem HCl)



A FAVORABLE HEMODYNAMIC PROFILE

Decreases peripheral vascular resistance, and does not compromise cardiac output[4]*†

Does not compromise renal blood flow and glomerular filtration rate and decreases renal vascular resistance[4-7]†

Increases coronary blood flow[1,3]

* As seen in patients with normal LV function. Caution should be used in patients with congestive heart failure.

† As seen in studies lasting up to 12 months. The effects of diltiazem on these renal and cardiovascular parameters past 12 months are unknown.

NEW

RARELY CAUSES ADVERSE METABOLIC EFFECTS

No significant changes in total cholesterol and triglycerides[1]

Rarely causes adverse effects on glucose or electrolytes[1,2,8‡]

DOSING INFORMATION

Available as 180-, 240-, and 300-mg dosage strengths

For new patients starting on Cardizem CD:

- Start with one 180-mg capsule daily
- Monitor for 2 weeks; if optimal response is not met
- Titrate to goal blood pressure

For patients switching from Cardizem SR:

- Switch on a total mg/day basis
- If necessary, titrate to goal blood pressure

Once-A-Day



180-mg capsules



240-mg capsules



300-mg capsules

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONE TO TRUST FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

‡ The incidence of hyperglycemia reported with diltiazem has been <1%.

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NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONCE A DAY

ONE TO TRUST

FOR MILD TO MODERATE HYPERTENSIVE PATIENTS

BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.



ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

Product Information as of October 1991

References: **1.** Data on file, Marion Merrell Dow Inc. **2.** Andrén L, Hoglund P, Dotevall A, et al. *Am J Cardiol.* 1988;62:114G-120G. **3.** O'Rourke RA. *Am J Cardiol.* 1985;56:34H-40H. **4.** Amodeo C, Kobrin I, Ventura HO, Messerli FH, Frohlich ED. *Circulation.* 1986;73(1):108-113. **5.** Demarie BK, Bakris GL. *Ann Intern Med.* 1990;113(12):987-988. **6.** Sundernrajan S, Reams G, Bauer JH. *Am Heart J.* 1987;114:383-388. **7.** Isshiki T, Amodeo C, Messerli FH, Pegram BL, Frohlich ED. *Cardiovascular Drugs and Therapy.* 1987;1:359-366. **8.** Frishman WH, Zawada ET Jr, Smith LK, et al. *Am J Cardiol.* 1987;59:615-623.

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KANSAS CITY, MO 64114

Long-Term Prognosis After Acute Myocardial Infarction in Patients with Left Ventricular Hypertrophy on the Electrocardiogram

Solomon Behar, MD, Henrietta Reicher-Reiss, MD, Edward Abinader, MD, Jacob Agmon, MD, Jacob Barzilai, MD, Yaacov Friedman, MD, Elieser Kaplinsky, MD, Nissim Kauli, MD, Yehezkiel Kishon, MD, Abraham Palant, MD, Benyamin Peled, MD, MSc, Leonardo Reisin, MD, Zwi Schlesinger, MD, Izhar Zahavi, MD, Monty Zion, MD, Uri Goldbourt, PhD, and the SPRINT Study Group*

Among 4,720 consecutive hospital survivors from acute myocardial infarction (AMI) treated in 13 coronary care units between July 1981 and August 1983, the estimated prevalence of electrocardiographic left ventricular (LV) hypertrophy was 6.1%. The prevalence of electrocardiographic LV hypertrophy increased with age and was higher in patients with previous myocardial infarction, angina and systemic hypertension. Mean age of patients with electrocardiographic LV hypertrophy was 67.2 vs 61.4 years in counterparts free of electrocardiographic LV hypertrophy. Patients with electrocardiographic LV hypertrophy had a higher rate of congestive heart failure on admission, or developing during their stay in coronary care units. The 1- and 5-year mortality rates were 19.7 and 46.6% among patients with electrocardiographic LV hypertrophy versus 8.7 and 26.2%, respectively ($p < 0.001$) in patients without this finding. The covariate-adjusted odds ratio of 1-year mortality was 1.88 for the presence of electrocardiographic LV hypertrophy when age alone was adjusted for, and 1.51 (90% confidence interval, 1.09 to 2.10) when multiple covariate adjustment was undertaken. After multiple covariate adjustment for 5-year mortality after discharge, the relative risk associated with electrocardiographic LV hypertrophy was 1.51 (90% confidence interval, 1.26 to 1.80). The results of the present study showed that the presence of electrocardiographic LV hypertrophy on the discharge electrocardiogram of survivors from AMI is associated with a 1.5-fold increase of short- and long-term mortality. Patients with electrocardiographic LV hypertrophy, potentially at an increased post-discharge risk, may be candidates for early noninvasive testing and more intensive follow-up after recovering from AMI.

(Am J Cardiol 1992;69:985–990)

Studies of prognosis after acute myocardial infarction (AMI) identified arrhythmias, conduction disturbances and ST-segment shifts on the discharge electrocardiogram as independent predictors of subsequent coronary morbidity and mortality.[1-5] Electrocardiographic left ventricular (LV) hypertrophy has also been identified as an important independent risk factor for predicting cardiac death, after both Q-wave and non-Q-wave AMI.[6,7] However, evaluation of the prognosis of electrocardiographic LV hypertrophy after AMI has been limited by relatively small numbers of such patients, or by possible patient selection bias.

In this study, we present an analysis of the prognostic significance of LV hypertrophy on the electrocardiogram in a large consecutive unselected cohort of 4,808 survivors after AMI from the Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) Registry.

METHODS

Study population: During 1981 to 1983, we conducted a secondary prevention study in which nifedipine was administered to 2,276 survivors of AMI hospitalized in 14 of 21 existing coronary care units in Israel at that time.[8] Nifedipine administration had no effect on the rate of clinical events.[9]

During the study period a logbook of all patients with AMI hospitalized in the coronary care units of 13 of the participating hospitals was maintained (SPRINT Registry, n = 5,839). Demographic, historical and medical data were collected on special forms. Mortality follow-up was complete up to 1988 for 99% of all hospital survivors (n = 4,808; mean 5.5 years). The diagnosis of AMI was based on typical clinical symptoms lasting ≥30 minutes, unequivocal Q/QS and ST-T changes on the electrocardiogram and high enzymatic levels (creatinine kinase, glutamic oxalotransaminase and lactate dehydrogenase). The hospital electrocardiograms were interpreted by 2 cardiologists according to the Minnesota code.[10] Electrocardiographic LV hypertrophy (Min-

From the Neufeld Cardiac Research Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel. The collection of the SPRINT Registry data was supported by a research grant from Bayer AG, Wuppertal, Germany, within the framework of the SPRINT Study. Manuscript received May 9, 1991; revised manuscript received and accepted December 18, 1991.

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*See Appendix for the list of participants in the SPRINT Study Group.

TABLE I Characteristics of Patients with Originally Diagnosed Versus Newly Detected Electrocardiographic Left Ventricular Hypertrophy

	Original (n = 187)		New (n = 21)		
	No.	%	No.	%	p Value
Men	117	63	10	48	NS
Age (mean year)	66.7 ± 10.0		71.6 ± 7.8		0.03
History					
AMI	63	34	6	29	NS
AP	107	57	11	52	NS
Hypertension	95	51	7	33	NS
Diabetes mellitus	35	19	3	14	NS
Mortality					
1 year	35	19	6	29	NS
5 years	86	46	11	52	NS

AMI = acute myocardial infarction; AP = angina pectoris; NS = not significant.

nesota codes 31, 33) was diagnosed in 187 patients (see Appendix 1).

For the purpose of the present study the filed predischarge electrocardiogram of all patients with diagnosed electrocardiographic LV hypertrophy and an additional 1,000 randomly selected electrocardiograms (±20% of the total population) were reassessed by one of us (SB) for diagnostic completeness and accuracy. Twenty-one new cases of electrocardiographic LV hypertrophy were diagnosed among the 1,000 randomly screened electrocardiograms (2.1%). Consequently, the prevalence rate of electrocardiographic LV hypertrophy in this study has to be augmented by approximately 2% to give an estimated actual prevalence. Overall, their history and especially the postdischarge mortality of the newly diagnosed patients with electrocardiographic LV hypertrophy did not differ significantly from those of the "original" patients, and they were therefore added to the electrocardiographic LV hypertrophy group for morbidity and mortality comparison with patients without electrocardiographic LV hypertrophy (Table I). Eighty-eight patients were excluded from the analysis because the predischarge electrocardiograms were missing.

Statistical analysis: Age-adjusted prevalence of attributes correlating with electrocardiographic LV hypertrophy was calculated. Multivariate logistic analysis of hospital and postdischarge mortality yielded estimates of the covariate-adjusted predictive power of electrocardiographic LV hypertrophy on early (in-hospital) and 1-year mortality. The SAS software[11] was used, specifically the FREQ and CATMOD procedures. The covariate-adjusted relative risks of mortality through mid-1988 (an average 5.5-year follow-up) were calculated using the proportional hazards analysis, procedure PHGLM of SAS.[12]

RESULTS

The prevalence of *identified* electrocardiographic LV hypertrophy among the SPRINT Registry survivors before adjustment on the basis of sample reassessment (see Methods) was 4.4% (208 of 4,720). Prevalence was more than double in women (7.4%) compared with men (3.5%) ($p < 0.001$) and increased significantly with age. It was also more prevalent among patients with previous

TABLE II Characteristics of Patients With and Without Electrocardiographic Left Ventricular Hypertrophy

	Present (n = 208)		Absent (n = 4,512)		
	No.	%	No.	%	p Value
Men	127	61.1	3,499	77.5	0.0001
Age (mean year)	67.2 ± 9.8		61.4 ± 10.6		0.0001
≤49	8	3.9	634	14.1	
50–59	35	16.8	1,219	27.0	
60–69	72	34.6	1,554	34.4	
≥70	93	44.7	1,105	24.5	
History					
AMI	69	33.2	967	21.4	0.0001
Angina pectoris	118	56.7	2,133	47.3	0.01
Systemic hypertension	102	49.0	1,793	39.7	0.01
Diabetes mellitus	38	18.3	877	19.4	NS
Smokers	48	23.1	1,645	36.5	0.0001
Chronic renal failure	20	9.6	164	3.6	0.0001
Cerebrovascular accident	20	9.6	170	3.8	0.0001
Enzymes > 4/normal					
CK	102	49.0	2,520	55.8	0.05
GOT	75	36.1	1,830	40.6	NS
LDH	25	12.0	508	11.3	NS
AMI location					
AMI Q-wave					<0.05
Anterior	70	33.7	1,905	42.2	
Inferior	88	42.3	1,843	40.8	
Lateral	9	4.3	216	4.8	
Undetermined	12	5.8	182	4.0	
Non-Q-AMI	29	13.9	366	8.1	0.01

AMI = acute myocardial infarction; CK = creatine kinase; GOT = glutamic oxaloacetic transaminase; LDH = lactate dehydrogenase; NS = not significant.

TABLE III Hospital Course of Patients With and Without Electrocardiographic Left Ventricular Hypertrophy

	Present (n = 208)		Absent (n = 4,512)		
	No.	%	No.	%	p Value
On admission					
Congestive heart failure	71	34.1	803	17.8	0.0001
Chest x-ray					
Pulmonary congestion	56	26.9	833	18.5	0.002
Cardiomegaly	89	42.8	1,145	25.4	0.0001
In-hospital					
Cardiac arrest	6	2.9	38	0.8	0.002
Ventricular fibrillation	9	4.3	176	3.9	NS
Ventricular tachycardia	23	11.1	738	16.4	0.04
Paroxysmal atrial fibrillation	28	13.5	510	11.3	NS
Advanced atrioventricular block	25	12.0	346	7.7	0.02
Congestive heart failure	46	22.1	745	16.5	0.03
Papillary muscle dysfunction	7	3.4	90	2.0	NS

NS = not significant.

AMI, angina pectoris and systemic hypertension before AMI, and among nonsmokers. Patients with non-Q-wave AMI had a prevalence of LV hypertrophy of 7.3% vs 4.3% in those with Q-wave AMI ($p < 0.005$). The characteristics of patients with and those without electrocardiographic LV hypertrophy are listed in Table II. Patients with electrocardiographic LV hypertrophy were older, included more women and had higher rates of previous AMI, angina, hypertension, cerebrovascular accidents and chronic renal disease. The frequency of very high serum enzyme levels (>4 times the upper normal limits) was similar in both groups. Smokers and anterior AMI location were found more often among patients without than with electrocardiographic LV hypertrophy.

The hospital course of both groups is summarized in Table III. Congestive heart failure and signs of cardiomegaly as well as pulmonary congestion on admission chest x-ray occurred more often with than without electrocardiographic LV hypertrophy. Cardiac arrest and ventricular tachycardia were more common in patients with LV hypertrophy, as were advanced atrioventricular block and the development of congestive heart failure after admission. Papillary muscle dysfunction occurred during the acute phase of myocardial infarction in 3.4% of patients with LV hypertrophy.

Postdischarge mortality in patients with electrocardiographic LV hypertrophy was significantly higher than in other survivors (Figure 1). One and 5-year postdischarge mortality rates were significantly higher in patients with electrocardiographic LV hypertrophy than in patients without these findings on the electrocardiograph (See Table IV). The modes of death over 1 year are presented in Table V. A slightly higher rate of sudden death was noted among patients with than without electrocardiographic LV hypertrophy, but this difference was not statistically significant.

To assess the independent association between electrocardiographic LV hypertrophy and mortality, multiple logistic regression was performed: (1) with electrocardiographic LV hypertrophy and age alone as the independent variables; and (2) adjusting, in addition to age, for gender, congestive heart failure (on admission or developing in the coronary care unit), history of AMI, angina and cerebrovascular accident, participation in the SPRINT trial, elevated serum enzyme levels and the site of infarct. The covariate-adjusted odds ratio for 1-year mortality was 1.88 for the presence of LV hypertrophy when age alone was adjusted (90% confidence interval [CI], 1.38 to 2.56) and 1.51 (90% CI, 1.09 to 2.10) when multiple covariate adjustment was undertaken. The latter odds ratio resembled those obtained for past cerebrovascular accident (1.53) and a 10-year age increment (1.61). In a multivariate analysis of the 5-year mortality, the relative risk for mortality in the presence of LV hypertrophy was 1.63 after age-adjustment (90% CI, 1.37 to 1.94) and 1.51 (90% CI, 1.26 to 1.80) after multiple covariate adjustment.

DISCUSSION

In the present study the estimated prevalence of electrocardiographic LV hypertrophy among 4,720 survivors was 6.1%. The data are in accordance with the prevalence of electrocardiographic LV hypertrophy among 2,122 subjects of the Rochester Epidemiology project (4.2%)[13] and among hypertensive patients from the Honolulu Study (5%),[14] but not with the data of the diltiazem study[7] in which as many as 23% of patients with a non-Q-wave AMI exhibited electrocardiographic LV hypertrophy. In the Framingham Study and the Coronary Drug Project, only 6.8 and 6.7%, respectively, of patients with Q-wave AMI had LV hypertrophy on the follow-up electrocardiogram.[6,15] Higher prevalence of electrocardiographic LV hypertrophy was strongly related in our study to gender (women), older age, history of previous MI, hypertension and non-Q-wave AMI in the index infarction. Patients with electrocardiographic LV hypertrophy had a higher incidence of complicated course during hospitalization. The proportion of patients with very high levels of serum cardiac

enzymes was, however, not increased among survivors with electrocardiographic LV hypertrophy. In the diltiazem study patients with electrocardiographic LV hypertrophy exhibited lower peak creatine kinase levels than patients without electrocardiographic LV hypertrophy.[7] Electrocardiographic LV hypertrophy was less frequently associated with anterior AMI. No obvious explanation is available for this difference. It is possible that AMI of anterior location conceals preexisting high R waves in the precordial leads. Non-Q-wave AMI was seen more frequently (13.9%) in patients with than without (8.1%) electrocardiographic LV hypertrophy ($p < 0.01$). This difference is compatible with a pathologic analysis of 204 patients with single AMI, in which Pirolo et al[16] found that larger heart weight and degree of LV hypertrophy had a significant negative correlation with infarct extension and that the degree to which an infarct expands may be influenced by the preinfarction thickness of the ventricular wall.

In several studies electrocardiographic LV hypertrophy was an independent risk factor for increased coronary and sudden death, congestive heart failure, stroke and AMI.[1-7,17-19] Resting 12-lead electrocardiograms in 251 survivors of clinically recognized Q-wave AMI in the Framingham study were examined in relation to reinfarction and coronary death over 32 years (mean follow-up 10.1 years).[6] Electrocardiographic LV hyper-

TABLE IV One- and Five-Year Mortality

	Electrocardiographic Left Ventricular Hypertrophy				
	Present (n = 208)		Absent (n = 4,512)		
	No.	%	No.	%	p Value
1 year	41	19.7	391	8.7	<0.0001*
5 years	97	46.6	1,180	26.2	<0.0001*

*Analyses using multiple covariate adjustment yielded an odds ratio of 1.51 for 1-year mortality, and a relative risk of 1.51 for 5-year mortality.

TABLE V One-Year Mode of Death

	Electrocardiographic Left Ventricular Hypertrophy				
	Present (n = 41)		Absent (n = 391)		
	No.	%	No.	%	p Value
Sudden death	21	51.2	177	45.3	NS
Cardiac death	13	31.7	122	31.2	
Noncardiac death	6	14.6	79	20.2	
Unknown	1	2.4	13	3.3	

NS = not significant.

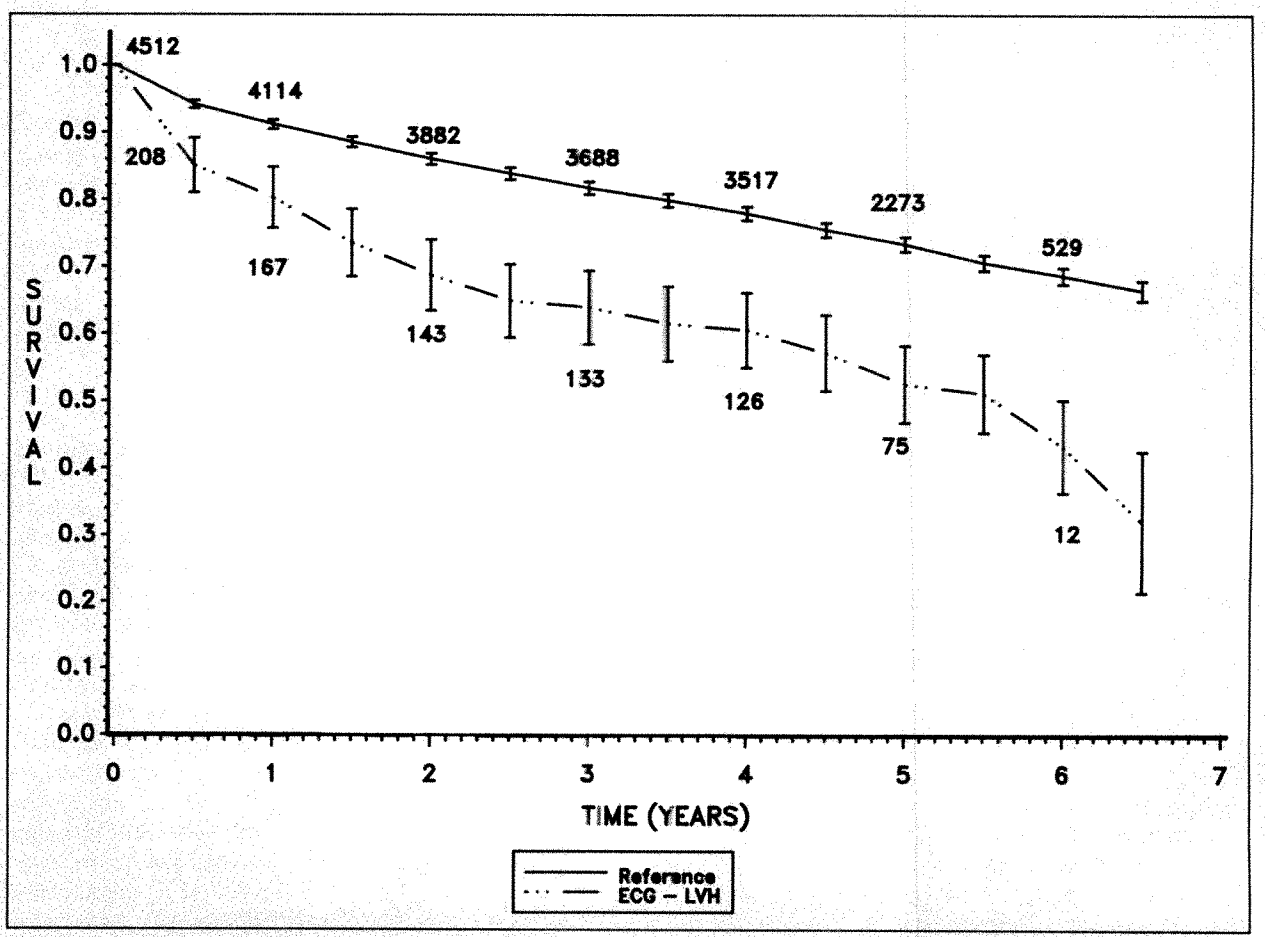


FIGURE 1. Five-year postdischarge survival curve in patients with and without electrocardiographic left ventricular hypertrophy (ECG – LVH).

trophy was a powerful predictor of coronary death, which increased between 2.7- and 3.5-fold compared with that of patients without electrocardiographic LV hypertrophy. However, the presence or absence of LV hypertrophy in the electrocardiogram was unrelated to the risk of reinfarction. In the diltiazem study,[7] 23% of patients with non-Q-wave AMI had LV hypertrophy using standard voltage criteria. Compared with patients without electrocardiographic LV hypertrophy, patients with non-Q-wave AMI and electrocardiographic LV hypertrophy had a twofold increased incidence of reinfarction (24 vs 12%) and death (19 vs 9%). In the Coronary Drug Project placebo group,[14] electrocardiographic LV hypertrophy, although associated with increased subsequent mortality, was not independently related to higher mortality at 3-year follow-up.

In our study, the 1-year mortality of survivors from AMI with electrocardiographic LV hypertrophy was double (19.7%) that of survivors without LV hypertrophy (8.7%) ($p < 0.0001$). These rates closely resemble those of the diltiazem study (19 and 9%, respectively).[7] After covariate adjustment, a 51% mortality excess at 1 and 5 years remained. These findings are supported by a recent echocardiographic study,[20] in which LV hypertrophy carried a higher risk of subsequent mortality, independent of angiographically defined coronary anatomy and LV function.[19]

The data of our study do not lend themselves to examination of (1) the causes of LV hypertrophy, and (2) the precise mechanisms by which LV hypertrophy increases mortality. However, patients with electrocardiographic LV hypertrophy were older, and had significantly higher prevalence rates of previous AMI, and previous angina pectoris and hypertension, all of which may contribute to the development of LV hypertrophy.[19] Moreover, patients with electrocardiographic LV hypertrophy had a significant increase in the prevalence of cardiomegaly on the admission chest x-ray, compared with patients without electrocardiographic LV hypertrophy. This finding is in keeping with autopsy data from the Framingham study which indicated that a correlation exists between the degree of electrocardiographic LV hypertrophy and the weight of the heart, as well as the thickness of the left ventricle.[21] Additional reports have suggested that patients with coronary artery disease have larger LV mass, resulting from either dilatation of the LV cavity or compensatory segmental hypertrophy.[20,22] Recent echocardiographic studies have further demonstrated the power of LV mass as a prognostic factor.[20,23]

Sudden death, transient ischemia, reduced coronary reserve and reduced diastolic function have been the mechanisms most frequently offered to explain increased mortality in survivors of AMI with LV hypertrophy.[2,3,6,13,24-26] In our study, patients with electrocardiographic LV hypertrophy had an increased rate of sudden death, but the difference was not statistically significant.

The importance of the present study relates to the large number of consecutive patients studied and the accomplishment of long-term follow-up in 99% of the patients discharged from hospital. Biases related to omission of certain categories of AMI were unlikely to occur and generalization of results is justified for post-MI risk stratification. However, because 21 new cases of electrocardiographic LV hypertrophy were found in 1,000 randomly reassessed electrocardiograms of the reference group (2.1%), and the use of the postinfarction electrocardiograms introduced the possibility that patients with LV hypertrophy who had experienced large infarcts might have a falsely negative electrocardiographic designation, the true prevalence rate of electrocardiographic LV hypertrophy among survivors from AMI can only be estimated (6.1%). Nevertheless, the data firmly support previous findings that the presence of electrocardiographic LV hypertrophy in survivors from AMI should be viewed as an independent risk factor.

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APPENDIX 1

Minnesota code of electrocardiographic left ventricular hypertrophy: Code 3-1: R amplitude >26 mm in either V_5 or V_6, or R amplitude >20 mm in any of leads I, II, III, aVF or R amplitude >12 mm in lead aVL; Code 3-3 (optional code when 3-1 is not present): R amplitude >15 mm but ≤20 mm in lead I, or R amplitude in V_5 or V_6, plus S amplitude in V_1 >35 mm. ST-segment and T-wave changes were not mandatory for electrocardiographic LV hypertrophy diagnosis.

APPENDIX 2

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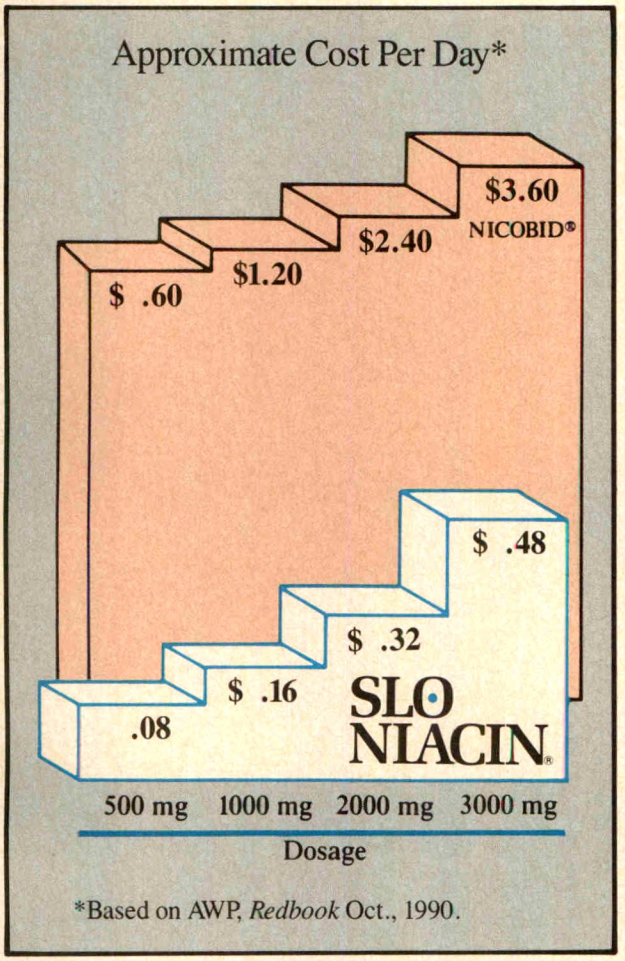
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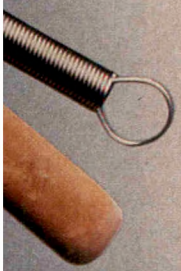
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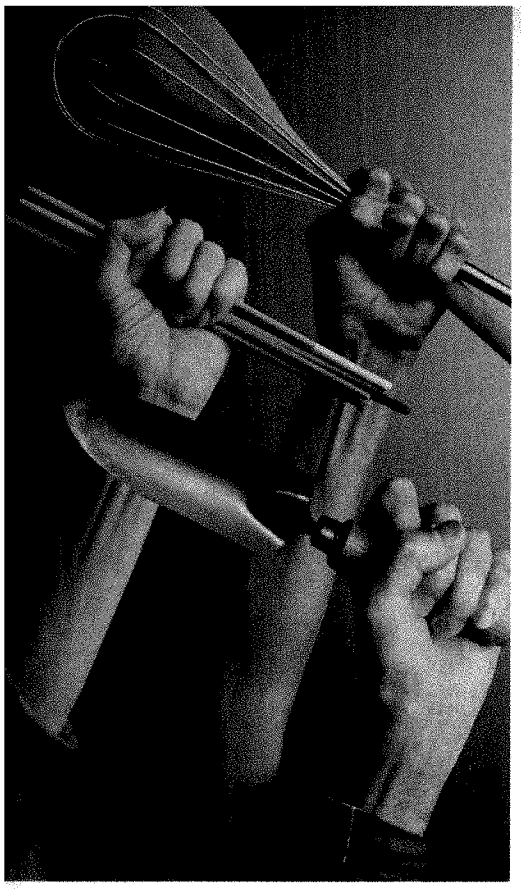
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Brief Summary

PROCARDIA XL® (nifedipine) Extended Release Tablets For Oral Use

CONTRAINDICATIONS: Known hypersensitivity reaction to nifedipine.

WARNINGS: Excessive Hypotension: Although in most angina patients the hypotensive effect of nifedipine is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine together with a beta-blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for nifedipine to be washed out of the body prior to surgery.

The following information should be taken into account in those patients who are being treated for hypertension as well as angina:

Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those who have severe obstructive coronary artery disease, have developed well documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of this effect is not established.

Beta Blocker Withdrawal: It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning nifedipine. Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of nifedipine treatment will not prevent this occurrence and on occasion has been reported to increase it.

Congestive Heart Failure: Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine. Patients with tight aortic stenosis may be at greater risk for such an event, as the unloading effect of nifedipine would be expected to be of less benefit to those patients, owing to their fixed impedance to flow across the aortic valve.

PRECAUTIONS: General—Hypotension: Because nifedipine decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of nifedipine is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See WARNINGS.)

Peripheral Edema: Mild to moderate peripheral edema occurs in a dose dependent manner with an incidence ranging from approximately 10% to about 30% at the highest dose studied (180 mg). It is a localized phenomenon thought to be associated with vasodilation of dependent arterioles and small blood vessels and not due to left ventricular dysfunction or generalized fluid retention. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Other: As with any other non-deformable material, caution should be used when administering PROCARDIA XL in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of PROCARDIA XL.

Laboratory Tests: Rare, usually transient, but occasionally significant elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted. The relationship to nifedipine therapy is uncertain in most cases, but probable in some. These laboratory abnormalities have rarely been associated with clinical symptoms; however, cholestasis with or without jaundice has been reported. A small (5.4%) increase in mean alkaline phosphatase was noted in patients treated with PROCARDIA XL. This was an isolated finding not associated with clinical symptoms and it rarely resulted in values which fell outside the normal range. Rare instances of allergic hepatitis have been reported. In controlled studies, PROCARDIA XL did not adversely affect serum uric acid, glucose, or cholesterol. Serum potassium was unchanged in patients receiving PROCARDIA XL in the absence of concomitant diuretic therapy, and slightly decreased in patients receiving concomitant diuretics.

Nifedipine, like other calcium channel blockers, decreases platelet aggregation *in vitro*. Limited clinical studies have demonstrated a moderate but statistically significant decrease in platelet aggregation and increase in bleeding time in some nifedipine patients. This is thought to be a function of inhibition of calcium transport across the platelet membrane. No clinical significance for these findings has been demonstrated.

Positive direct Coombs test with/without hemolytic anemia has been reported but a causal relationship between nifedipine administration and positivity of this laboratory test, including hemolysis, could not be determined.

Although nifedipine has been used safely in patients with renal dysfunction and has been reported to exert a beneficial effect in certain cases, rare reversible elevations in BUN and serum creatinine have been reported in patients with pre-existing chronic renal insufficiency. The relationship to nifedipine therapy is uncertain in most cases but probable in some.

Drug Interactions—Beta-adrenergic blocking agents: (See WARNINGS) Experience in over 1400 patients with Procardia® capsules in a noncomparative clinical trial has shown that concomitant administration of nifedipine and beta-blocking agents is usually well tolerated but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina.

Long Acting Nitrates: Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of nifedipine with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing nifedipine to avoid possible over- or under-digitalization.

Coumarin Anticoagulants: There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain.

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak nifedipine plasma levels (80%) and area-under-the-curve (74%), after a one week course of cimetidine at 1000 mg per day and nifedipine at 40 mg per day. Ranitidine produced smaller, non-significant increases. The effect may be mediated by the known inhibition of cimetidine on hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of nifedipine. If nifedipine therapy is initiated in a patient currently receiving cimetidine, cautious titration is advised.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Nifedipine was administered orally to rats, for two years and was not shown to be carcinogenic. When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose. *In vivo* mutagenicity studies were negative.

Pregnancy: Pregnancy Category C. Nifedipine has been shown to be teratogenic in rats when given in doses 30 times the maximum recommended human dose. Nifedipine was embryotoxic (increased fetal resorptions, decreased fetal weight, increased stunted forms, increased fetal deaths, decreased neonatal survival) in rats, mice, and rabbits at doses of from 3 to 10 times the maximum recommended human dose. In pregnant monkeys, doses 2/3 and twice the maximum recommended human dose resulted in small placentas and underdeveloped chorionic villi. In rats, doses three times maximum human dose and higher caused prolongation of pregnancy. There are no adequate and well controlled studies in pregnant women. PROCARDIA XL® (nifedipine) Extended Release Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE EXPERIENCES: Over 1000 patients from both controlled and open trials with PROCARDIA XL Extended Release Tablets in hypertension and angina were included in the evaluation of adverse experiences. All side effects reported during PROCARDIA XL Extended Release Tablet therapy were tabulated independent of their causal relation to medication. The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg). Other common adverse experiences reported in placebo-controlled trials include: headache (15.8%, compared to 9.8% placebo incidence), fatigue (5.9%, compared to 4.1% placebo incidence), dizziness (4.1%, compared to 4.5% placebo incidence), constipation (3.3%, compared to 2.3% placebo incidence), and nausea (3.3%, compared to 1.9% placebo incidence). Of these, only edema and headache were more common in PROCARDIA XL patients than placebo patients.

The following adverse reactions occurred with an incidence of less than 3.0%. With the exception of leg cramps, the incidence of these side effects was similar to that of placebo alone: *body as a whole/systemic*: asthenia, flushing, pain; *cardiovascular*: palpitations; *central nervous system*: insomnia, nervousness, paresthesia, somnolence; *dermatologic*: pruritus, rash; *gastrointestinal*: abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence; *musculoskeletal*: arthralgia, leg cramps; *respiratory*: chest pain (nonspecific), dyspnea; *urogenital*: impotence, polyuria.

Other adverse reactions were reported sporadically with an incidence of 1.0% or less. These include: *body as a whole/systemic*: face edema, fever, hot flashes, malaise, periorbital edema, rigors; *cardiovascular*: arrhythmia, hypotension, increased angina, tachycardia, syncope; *central nervous system*: anxiety, ataxia, decreased libido, depression, hypertonia, hypoesthesia, migraine, paronirla, tremor, vertigo; *dermatologic*: alopecia, increased sweating, urticaria, purpura; *gastrointestinal*: eructation, gastroesophageal reflux, gum hyperplasia, melena, vomiting, weight increase; *musculoskeletal*: back pain, gout, myalgias; *respiratory*: coughing, epistaxis, upper respiratory tract infection, respiratory disorder, sinusitis; *special senses*: abnormal lacrimation, abnormal vision, taste perversion, tinnitus; *urogenital/reproductive*: breast pain, dysuria, hematuria, nocturia.

Adverse experiences which occurred in less than 1 in 1000 patients cannot be distinguished from concurrent disease states or medications.

The following adverse experiences, reported in less than 1% of patients, occurred under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain: gastrointestinal irritation, gastrointestinal bleeding.

In multiple-dose U.S. and foreign controlled studies with nifedipine capsules in which adverse reactions were reported spontaneously, adverse effects were frequent but generally not serious and rarely required discontinuation of therapy or dosage adjustment. Most were expected consequences of the vasodilator effects of Procardia. Adverse experiences reported in placebo-controlled trials include: dizziness, lightheadedness, and giddiness (27%, compared to 15% placebo incidence); flushing, heat sensation (25%, compared to 8% placebo incidence); headache (23%, compared to 20% placebo incidence); weakness (12%, compared to 10% placebo incidence); nausea, heartburn (11%, compared to 8% placebo incidence); muscle cramps, tremor (8%, compared to 3% placebo incidence); peripheral edema (7%, compared to 1% placebo incidence); nervousness, mood changes (7%, compared to 4% placebo incidence); palpitation (7%, compared to 5% placebo incidence); dyspnea, cough, and wheezing (6%, compared to 3% placebo incidence); and nasal congestion, sore throat (6%, compared to 6% placebo incidence).

There is also a large uncontrolled experience in over 2100 patients in the United States. Most of the patients had vasospastic or resistant angina pectoris, and about half had concomitant treatment with beta-adrenergic blocking agents. The relatively common adverse events were similar in nature to those seen with PROCARDIA XL.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

In a subgroup of over 1000 patients receiving Procardia with concomitant beta blocker therapy, the pattern and incidence of adverse experiences was not different from that of the entire group of Procardia treated patients (See PRECAUTIONS.)

In a subgroup of approximately 250 patients with a diagnosis of congestive heart failure as well as angina, dizziness or lightheadedness, peripheral edema, headache or flushing each occurred in one in eight patients. Hypotension occurred in about one in 20 patients. Syncope occurred in approximately one patient in 250. Myocardial infarction or symptoms of congestive heart failure each occurred in about one patient in 15. Atrial or ventricular dysrhythmias each occurred in about one patient in 150.

In post-marketing experience, there have been rare reports of exfoliative dermatitis caused by nifedipine.

More detailed professional information available on request. Revised July 1990

Pfizer Labs

Milwaukee Prehospital Chest Pain Project — Phase I: Feasibility and Accuracy of Prehospital Thrombolytic Candidate Selection

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This study prospectively determined the feasibility and accuracy of prehospital thrombolytic therapy candidate selection by base station emergency physicians. During a 6-month period, paramedics acquired and transmitted prehospital 12-lead electrocardiograms (ECGs) and then applied a thrombolytic therapy contraindication checklist. Emergency physicians interpreted prehospital ECGs and prospectively selected candidates for thrombolytic therapy. A safety committee of cardiologists reviewed prehospital ECGs, checklists and hospital records to determine accuracy independently. Six hundred-eighty stable adult prehospital patients with a chief complaint of nontraumatic chest pain were initially evaluated. Two hundred forty-one patients were excluded because of (1) unsuccessful electrocardiographic transmission (149), (2) transport to nonparticipating facilities (72), and (3) unavailable medical records (20). No prehospital thrombolytic therapy was administered in this study. Of 439 cases, 91 (21%) had the final diagnosis of acute myocardial infarction, 38 (8.7%) had diagnostic prehospital ECGs, and 12 (2.7%) were selected by emergency physicians as candidates for thrombolytic therapy. Seventy percent of patients with myocardial infarction had checklist exclusions for thrombolytic therapy. Prehospital evaluation increased mean scene time (paramedic arrival on scene to scene departure) by 4 minutes. The median time from chest pain onset to paramedic arrival in patients with myocardial infarction was 60 minutes. The estimated average time saved if prehospital thrombolytic therapy had been available was 101 ± 81 minutes. The safety committee concluded that acceptable accuracy of emergency physician prehospital electrocardiographic interpretation, checklist and case selection was achieved. It is concluded that emergency physicians can accurately identify candidates for prehospital thrombolytic therapy.

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The Italian Group for the Study of Streptokinase in Myocardial Infarction, European Cooperative Study Group, the APSAC International Mortality Study trial, and others have demonstrated a clear relationship between early thrombolytic therapy and improved myocardial salvage and survival.[1–12] However, hospital-based time to treatment continues to remain long with a national average of 89 minutes in a recently reported study.[13] One possible approach to reduce time delays to treatment for patients with acute myocardial infarction (AMI) would be the initiation of thrombolytic therapy in the prehospital setting.

This study determines the accuracy of base station emergency physician prehospital thrombolytic candidate selection (including base physician prehospital electrocardiographic interpretation and paramedic checklist detection of historical contraindications to thrombolytic therapy). A secondary end point of the study was to estimate potential time saved if prehospital thrombolytic therapy had been available.

METHODS

The Milwaukee County emergency medical system serves a population of approximately 1,000,000 people covering an area of 240 square miles. Ten paramedic-staffed ambulances operate under a single base station controlled by emergency physicians at the Milwaukee County Medical Complex. Base physicians in this study were second-, third- or fourth-year emergency medicine residents with academically trained and board-certified emergency medicine faculty who supervised 12-lead electrocardiographic interpretation and were responsible for prospective selection of prehospital thrombolytic candidates.

All 10 Milwaukee County paramedic rigs were equipped with computerized, portable Marquette Electronics MAC PC 12-lead electrocardiographs, coupled with cellular telephone transmission capability. This technology provides a printed copy of the 12-lead electrocardiogram (ECG) at the paramedic site, while simultaneously transmitting an ECG to a receiving unit at the centralized base station. The transmission of prehospital 12-lead ECGs has been previously demonstrated to be accurate and reliable.[14]

A 20-item paramedic checklist designed to identify relative and absolute contraindications to prehospital treatment with tissue-type plasminogen activator was developed for this study (Figure 1). Prehospital check-

list criteria were more restrictive than hospital-based criteria (e.g., excluding patients with any history of diabetes, liver or kidney problems). The checklist appropriately prevented paramedics from exercising clinical judgment in the case selection process.

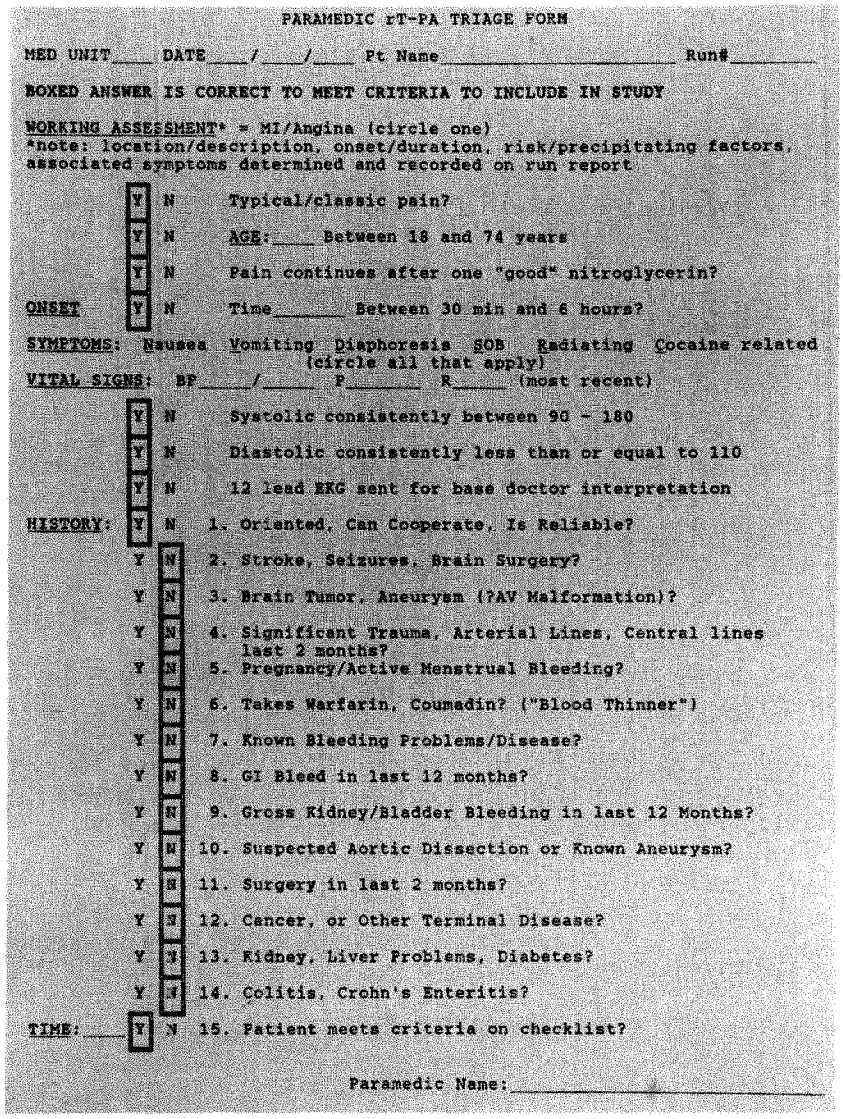
After conducting a history and physical examination, paramedics acquired and transmitted a 12-lead ECG to the base station emergency physician as the first step in the case selection process. This allowed the base physician to incorporate the information from prehospital 12-lead ECGs in the treatment and care of the patient. During prehospital treatment or transport, paramedics completed the 20-item checklist for relative or absolute contraindications to thrombolytic therapy. This information was communicated by paramedics to the emergency medicine faculty base physician who prospectively selected candidates for thrombolysis.

No thrombolytic therapy was administered in the field during this study. Instead, a decision was made by the faculty base physician whether or not the patient was eligible and would have received prehospital thrombolytic therapy if it had been available.

A safety committee of 11 cardiologists from the 8 participating hospitals retrospectively reviewed hospital and prehospital charts and ECGs on a monthly basis throughout the study to determine independently the accuracy of the selection process. Unlike base station emergency physicians, the cardiologists had access to the patient's hospital record, including prior 12-lead ECGs for comparison.

Cooperative (alert and oriented, able to speak and comprehend English, able to cooperate with prehospital treatment, and perceived by paramedics as reliable), stable (systolic blood pressure >90 mm Hg, and the absence of ventricular tachycardia, ventricular fibrillation, second- or third-degree heart block), adult (>18 years old) patients who sought paramedic evaluation for a chief complaint of nontraumatic chest pain of presumed ischemic origin were considered eligible for the study. Patients with chest pain were excluded if, in the opinion of the paramedic, the acquisition of prehospital study information would interfere with patient care.

Minimal electrocardiographic criteria for consideration of the diagnosis of AMI was defined as ≥1 mm of



PARAMEDIC rT-PA TRIAGE FORM

MED UNIT____ DATE___/___/___ Pt Name_____ Run#_____

BOXED ANSWER IS CORRECT TO MEET CRITERIA TO INCLUDE IN STUDY

WORKING ASSESSMENT* = MI/Angina (circle one)
*note: location/description, onset/duration, risk/precipitating factors, associated symptoms determined and recorded on run report

[Y] N Typical/classic pain?

[Y] N AGE:___ Between 18 and 74 years

[Y] N Pain continues after one "good" nitroglycerin?

ONSET [Y] N Time_____ Between 30 min and 6 hours?

SYMPTOMS: Nausea Vomiting Diaphoresis SOB Radiating Cocaine related
(circle all that apply)

VITAL SIGNS: BP____/____ P_____ R____ (most recent)

[Y] N Systolic consistently between 90 - 180

[Y] N Diastolic consistently less than or equal to 110

[Y] N 12 lead EKG sent for base doctor interpretation

HISTORY: [Y] N 1. Oriented, Can Cooperate, Is Reliable?

Y [N] 2. Stroke, Seizures, Brain Surgery?

Y [N] 3. Brain Tumor, Aneurysm (?AV Malformation)?

Y [N] 4. Significant Trauma, Arterial Lines, Central lines last 2 months?

Y [N] 5. Pregnancy/Active Menstrual Bleeding?

Y [N] 6. Takes Warfarin, Coumadin? ("Blood Thinner")

Y [N] 7. Known Bleeding Problems/Disease?

Y [N] 8. GI Bleed in last 12 months?

Y [N] 9. Gross Kidney/Bladder Bleeding in last 12 Months?

Y [N] 10. Suspected Aortic Dissection or Known Aneurysm?

Y [N] 11. Surgery in last 2 months?

Y [N] 12. Cancer, or Other Terminal Disease?

Y [N] 13. Kidney, Liver Problems, Diabetes?

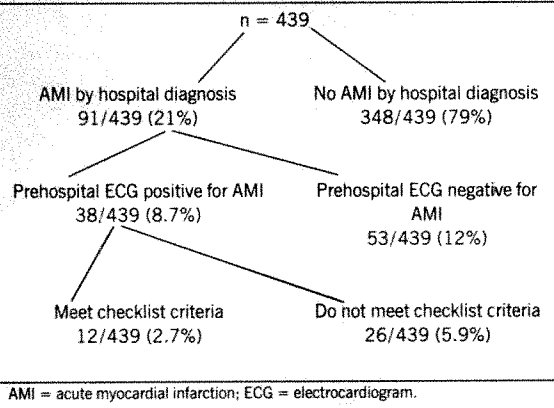
Y [N] 14. Colitis, Crohn's Enteritis?

TIME:___ [Y] N 15. Patient meets criteria on checklist?

Paramedic Name:_____

FIGURE 1. Paramedic recombinant tissue-type plasminogen activator (rT-PA) triage form. AV = arteriovenous; BP = blood pressure; EKG = electrocardiogram; GI = gastrointestinal; MI = myocardial infarction; P = pulse; R = respiration; SOB = shortness of breath.

TABLE I Patients with Evaluated Prehospital Chest Pain



AMI = acute myocardial infarction; ECG = electrocardiogram.

ST-segment elevation in ≥2 anatomically adjacent leads.

The final hospital diagnosis was determined by the safety committee investigators. The final hospital diagnosis of AMI required meeting World Health Organization criteria for clinical history, ECG and cardiac enzyme tests. The final hospital diagnosis of angina pectoris included new-onset, unstable and stable angina pectoris, and was made by the safety committee investigators after hospital chart review and the treating physician's diagnosis. Patients without evidence of AMI or angina pectoris after review of hospital records were classified as nonischemic.

Standardized verbal consent was obtained by paramedics before study entry. This project was approved by the Human Research Review Committee of the Medical College of Wisconsin.

Student's *t* test was used to evaluate mean ± standard deviation. Fischer's exact test was used for statistical comparison of ratios. P values were considered significant at <0.05.

RESULTS

During a 6-month period, from July 17, 1989, through January 1, 1990, the Milwaukee paramedics attempted to acquire prehospital 12-lead ECGs on 680 stable patients complaining of nontraumatic chest pain. There were 149 (22%) unsuccessful cellular transmissions of the ECG which were excluded from the study. Also excluded were 72 patients (14%) transported to nonparticipating facilities and 20 patients (4%) whose medical record was not available for review.

Of the 439 patients reviewed, 91 (21%) had a final discharge diagnosis of AMI, whereas 148 (34%) were discharged with a diagnosis of angina. The remaining 200 (45%) had diagnoses that were nonischemic.

The patient population (n = 439) consisted of 202 men (46%) and 236 women (54%) aged 27 to 94 years. The average age of men was 64 ± 14 years and that of females 67 ± 15 years. Women with a final hospital diagnosis of AMI were significantly older than men with a final hospital diagnosis of AMI (74 ± 10 vs 65 ± 13 years, p <0.001).

TABLE II Incidence of Relative and Absolute Contraindications to Prehospital Thrombolytic Therapy by Paramedic Checklist

	Final Hospital Diagnosis		
	AMI	Angina	Nonischemic
Age >74 years	44	42	31
Systolic <90 or >180 mm Hg	25	23	20
Chest pain onset >6 hours	22	12	26
Kidney or liver disease/diabetes	20	19	21
Atypical chest pain	14	12	23
Trauma/arterial or central lines/surgery in last 2 months	9	12	12
Stroke/seizures/brain surgery	8	10	11
Known bleeding problems/disease	8	5	3
Diastolic >100 mm Hg	5	13	10
Chest pain relieved by 1 NTG	5	16	20
Disoriented/incommunicative	5	5	6
Brain tumor/aneurysm	3	2	0.6
Takes warfarin	3	12	13
Gastrointestinal bleed in last 12 months	3	4	5
Kidney/bladder bleeding in last 12 months	3	2	3
Cancer or other terminal illness	3	3	11
Suspected aortic dissection or known aneurysm	1.5	2	1
Colitis/Crohn's enteritis	1.5	2	2
Pregnancy/active menstrual bleeding	0	0	2.5
Percent of patients with 1 or more contraindications	70	82	79

AMI = acute myocardial infarction; NTG = nitroglycerin.

Of the 439 patients in the study population, 91 (21%) had the final hospital diagnosis of AMI, 38 (8.7%) had transmitted prehospital 12-lead ECGs diagnostic for AMI, and 12 (2.7%) met checklist criteria and were selected as candidates for prehospital thrombolytic therapy by base station emergency physicians (Table I).

The frequency of relative and absolute contraindications to prehospital tissue-type plasminogen activator in patients with a final hospital diagnosis of AMI, angina and nonischemic chest pain is presented in Table II. There were no cases of paramedic failure to identify absolute or relative contraindications.

The mean scene time (paramedic arrival on scene to scene departure) for the entire study population was 29 ± 7 minutes. To determine if the acquisition of study information unacceptably prolonged scene time, a retrospective control group of 442 patients with chest pain seen by paramedics during a 6-month period before the onset of the study was established. Retrospective control patients without study interventions were matched for the following study group characteristics: (1) coopera-

TABLE III Times*

	Minutes
Scene delay (29 ± 7 vs 25 ± 6 minutes) (n = 439)	4
Chest pain onset to paramedic arrival in patients with AMI (n = 91)	60
Prehospital 12-lead acquisition of ECG (n = 439)	10 ± 7
Emergency department acquisition of 12-lead ECG (n = 439)	19 ± 18
Time from prehospital to hospital 12-lead ECG (n = 439)	47 ± 21
Estimated time saved with prehospital initiation of thrombolytic therapy (n = 6)	101 ± 81

*All times are mean times except item 2, which is expressed as median time.
AMI = acute myocardial infarction; ECG = electrocardiogram.

tive (alert and oriented, cooperative with prehospital treatment); (2) stable (systolic blood pressure >90 mm Hg, and the absence of ventricular tachycardia, ventricular fibrillation, second- or third-degree heart block on initial paramedic evaluation); (3) chief complaint of nontraumatic chest pain of presumed ischemic origin; (4) base physician contact and treatment; and (5) advanced cardiac life support transport. The mean scene time in this control population was 25 ± 6 minutes. The acquisition, transmission and interpretation of prehospital 12-lead ECGs by base physicians, along with the completion of the 20-item paramedic checklist and final decision to treat by the base physician, increased mean scene time over control by 4 minutes (Table III).

The median time from onset of chest pain to paramedic arrival in AMI patients was 60 minutes (range 5 minutes to 6 days). The mean time for prehospital 12-lead acquisition (time from paramedic arrival at patient to obtaining the 12-lead ECG) was 10 ± 7 minutes. Paramedics acquired prehospital 12-lead ECGs nearly twice as fast as receiving emergency departments. The time from paramedic arrival at the emergency department to emergency department 12-lead electrocardiographic acquisition was 19 ± 18 minutes ($p < 0.05$). The mean time elapsed from prehospital ECG to emergency department ECG was 47 ± 21 minutes. No statistically significant differences were seen between AMI, angina and nonischemic subgroups (Table III).

The potential time saved by prehospital initiation of thrombolytic therapy was estimated by determining the time elapsed between the prehospital decision to treat and the actual administration of hospital-based thrombolytic therapy. Twelve patients were selected by base station emergency physicians as candidates for prehospital thrombolytic therapy. Although correctly identified by emergency physicians, 6 of these 12 patients did not receive hospital-based thrombolytic therapy. Three patients were treated with emergent coronary angioplasty and 3 patients with inferior myocardial infarctions were managed conservatively without thrombolytic therapy or procedural intervention. The mean time from prehospital decision to treat and hospital-based administration of thrombolytic therapy in the remaining 6 patients (estimated potential time saved) was 101 ± 81 minutes (Table III).

Of the 38 patients with a prehospital 12-lead ECG interpreted as diagnostic for AMI by base station emergency physicians, 12 (32%) were selected as candidates for prehospital thrombolytic therapy. None had relative or absolute contraindications and all met World Health Organization criteria for the final hospital diagnosis of AMI. The safety committee confirmed a base physician thrombolytic candidate selection positive predictive value of 100%.

One patient received a false-positive electrocardiographic AMI diagnosis by emergency physicians but was not selected as a candidate for prehospital thrombolytic therapy because of historical contraindications. The ECG met all AMI study criteria and appeared morphologically identical to a hyperacute anterior AMI. Cardiology chart review revealed no change from prior 12-lead ECGs, and that this represented a left ventricular aneurysm sustained as the result of an old AMI. Because of this single but important case, the safety committee recommended excluding patients with a history of prior AMI from consideration for prehospital thrombolytic therapy (which would reduce eligible candidates by only 4%). The safety committee confirmed acceptable overall accuracy of emergency physician's electrocardiographic interpretation (which was not statistically different from that of cardiologists [Table IV]), and further recommended proceeding to the second phase of this project.

TABLE IV Diagnostic Accuracy of Prehospital 12-Lead Electrocardiographic Interpretation for Acute Myocardial Infarction (n = 439)

	Cardiologists			Base Physicians		
	AMI +	AMI −		AMI +	AMI −	p Value
ECG +	44	0		38	1	
ECG −	47	348		53	347	
Sensitivity	44/91 (48%)		Sensitivity	38/91 (42%)		NS
Specificity	348/348 (100%)		Specificity	347/348 (99.7%)		NS
PPV	44/44 (100%)		PPV	38/39 (97%)		NS
NPV	348/395 (88%)		NPV	347/400 (87%)		NS

AMI = acute myocardial infarction; ECG = electrocardiogram; NPV = negative predictive value; NS = not significant; PPV = positive predictive value; + = positive; − = negative.

DISCUSSION

Weaver et al[15] recently demonstrated the feasibility and safety of paramedic prehospital case selection for initiation of thrombolytic therapy in the Seattle emergency medical system. They devised a systematic protocol to select candidates for prehospital thrombolytic therapy by first including patients with presumed ischemic chest pain, followed by a paramedic-applied checklist of relative and absolute contraindications to thrombolytic therapy, and finally applying prehospital 12-lead ECGs to that clinical subset of patients who met these history, examination and checklist criteria. This systematic protocol appears very successful in accurately identifying such candidates, but excludes consideration of prehospital 12-lead electrocardiographic acquisition in >70% of evaluated cases.[15]

Compared with the Seattle Myocardial Infarction Triage and Intervention Project, our protocol required prehospital 12-lead electrocardiographic acquisition as the first step in the case selection process. The Milwaukee Prehospital Chest Pain Project has chosen this strategy based on previous data demonstrating significant advantages to obtaining prehospital ECGs in all cooperative, stable, adult patients with presumed ischemic chest pain.[16,17] Potential advantages include (1) improved prehospital diagnostic accuracy by base physicians for patients with AMI, angina, and nonischemic chest pain; (2) comparison of prehospital 12-lead ECGs with the first emergency department 12-lead ECG; (3) decreased hospital-based time delays in patients with documented prehospital ischemic events; and (4) potential for improved prehospital triage, treatment and transport decisions.[16–20] This approach allows incorporation of 12-lead electrocardiographic information in the treatment and prehospital decisions of nonthrombolytic candidates, while also allowing identification of patients for thrombolytic therapy. Despite having to carry the ECG machine to the scene in all cases, Milwaukee paramedics have been enthusiastic and receptive to this approach.[17]

Low numbers of candidates for selected thrombolytic therapy (12 of 439 or 2.7%) does not necessarily preclude consideration of prehospital thrombolytic therapy. Patient safety and diagnostic accuracy must be absolutely prioritized during these initial research protocols. The safety committee believed that base physicians were appropriately conservative in excluding 10 patients meeting minimally acceptable electrocardiographic criteria and an additional 7 patients in this study with relative contraindications who received hospital-based thrombolytic therapy. The number of eligible candidates for prehospital thrombolytic therapy may be safely increased in the future with more liberal electrocardiographic interpretation and checklist criteria. Furthermore, prehospital 12-lead ECGs may become standard in future emergency medical systems because of its value to nonthrombolytic candidates.[16,17] Initiation of prehospital thrombolytic therapy might be considered an additional benefit to patient care with implementation of prehospital 12-lead technology if the frequency of its occurrence is high enough to maintain paramedic skills.

The overall unsuccessful cellular transmission rate for this study was 22% (149 of 680 prehospital 12-lead ECGs). Monthly failed transmission rates were a high of 33% the first month of the study and a low of 11% later in the study, demonstrating a learning curve. Reasons for failed transmission included operator error, lack of proximity of the paramedic to a cellular telephone cell, interference from concrete and steel structures (particularly basements), system access during periods of peak use, and simultaneous transmission by 2 paramedic rigs to the same receiving unit. Implementation of an optional plug-in landline for use with on-scene touch-tone telephones combined with improved operator skills have reduced the cellular transmission failure rate to 10 to 15%.

The single centralized base station serving as medical control for this study was retrospectively viewed as important in achieving quality assurance. Eighteen emergency medicine residents and 12 academically trained and board-certified emergency physician faculty represented a manageable number of participants. This advantage may be diminished by emergency medical systems transmitting prehospital 12-lead ECGs to each receiving hospital.

The findings in this study are remarkably similar to the Myocardial Infarction Triage and Intervention Project feasibility study recently published by Weaver et al.[15] The successful completion of the Milwaukee Prehospital Chest Pain Project — Phase I may also indicate potential feasibility in other centers.

Administrative study design incorporating an independent safety committee involved the Milwaukee medical community from the very onset of the project, engendered confidence in the accuracy of the emergency medical system, and produced support for investigation of the concept of prehospital thrombolytic therapy.

Completing an initial "dry run" study provided our emergency medical system with the opportunity to identify and correct administrative, technical and quality assurance issues before initiating field thrombolysis. We recommend completion of similar studies in other emergency medical systems considering administration of prehospital thrombolytic therapy.

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APPENDIX

PARTICIPATING CLINICAL CENTERS: Milwaukee County Medical Complex, Columbia Hospital, St. Joseph's Hospital, St. Mary's Hospital, St. Michael's Hospital, West Allis Memorial Hospital, St. Luke's Hospital, and Sinai-Samaritan Medical Center.

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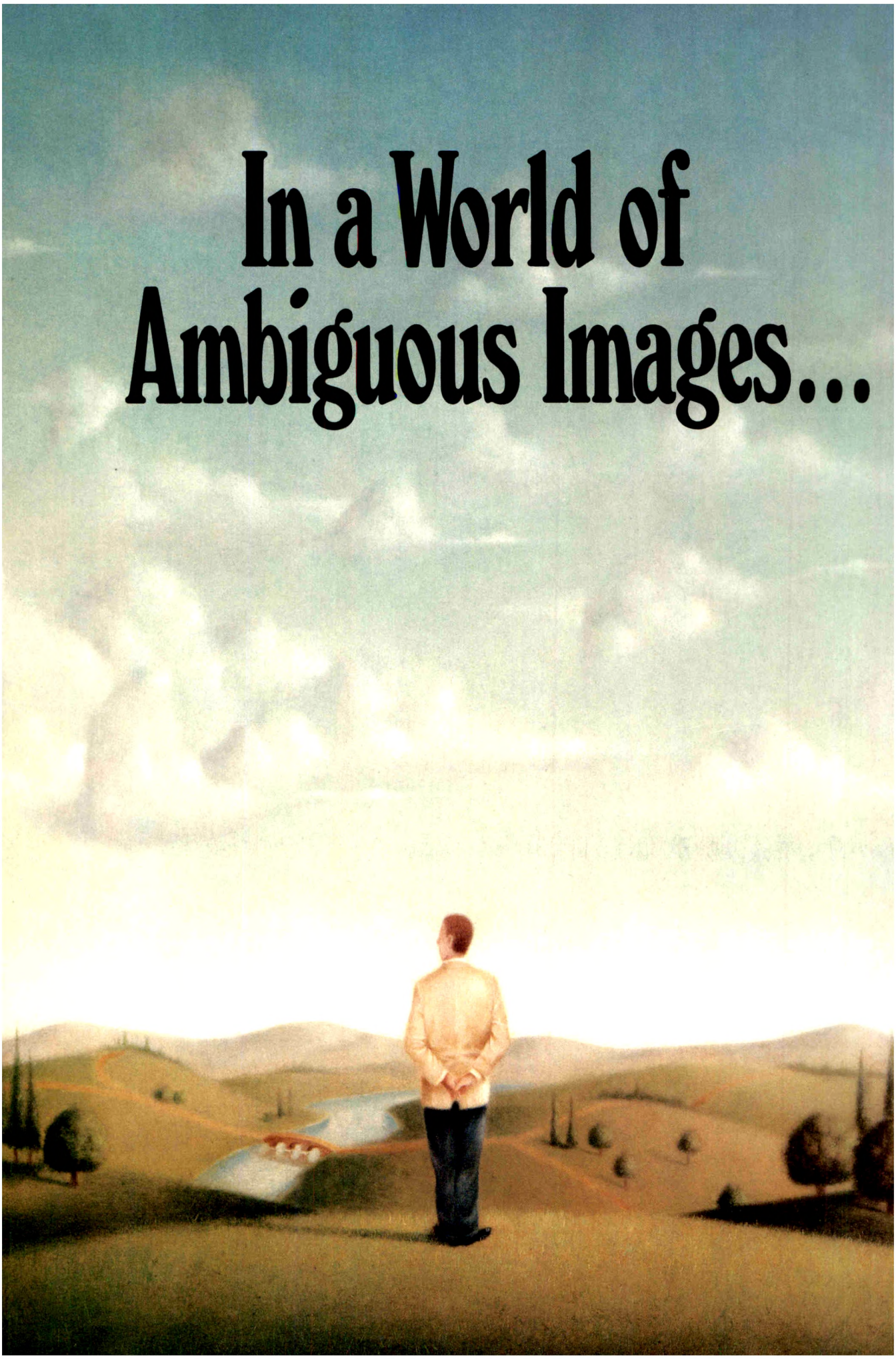
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All nonionic iodinated contrast media currently availa
inhibit blood coagulation, *in vitro*, less than ionic cont
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Therefore, meticulous intravascular administration te
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HOW ISOVUE®-370 PROVIDED MORE DETAILS THAN A 320-mg I/mL IODINE CONCENTRATION (HEXABRIX) IN PEDIATRIC CORONARY ANGIOGRAPHY[1]



A prospective crossover study compared the visualization of Isovue-370 with a low-osmolar 320-mg I/mL media in 26 children with Kawasaki disease. Three experienced clinicians who did not know which media had been used sorted the angiograms according to quality of image.

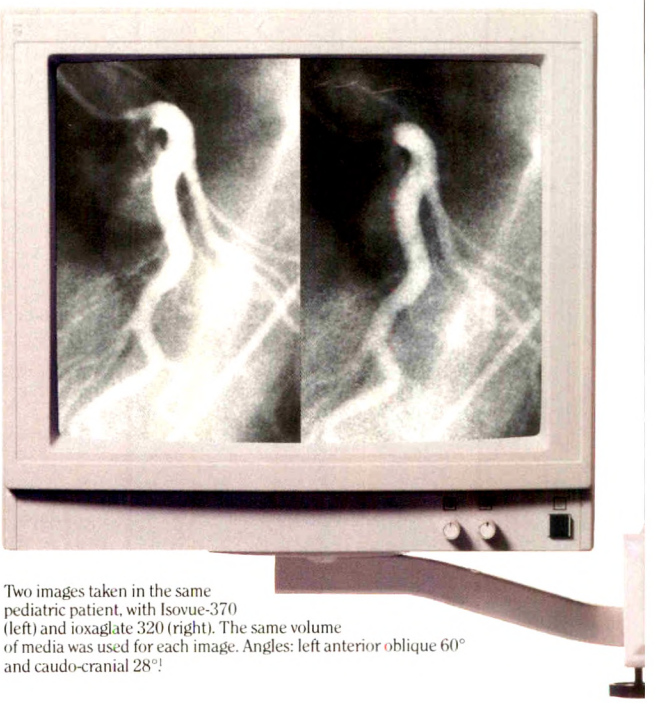
Twice as many Isovue-370 images were rated as having superior detail definition than those which used the 320-iodine concentration.[1]

Left Coronary Angiography: Evaluation of Visualization[1]			
Degree of Visualization	+3 (good contrast; easy diagnosis)	+2 (slightly poor contrast; relatively easy diagnosis)	+1 (poor contrast; diagnosis possible)
ISOVUE-370	**25**	**1**	**0**
Ioxaglate 320	12	14	0

Although both agents gave adequate visualization to make diagnosis, "...stenotic lesions were better visualized with iopamidol than with ioxaglate."[1]

Isovue-370 has the highest iodine concentration of any low-osmolar or nonionic contrast media, including Omnipaque (350 mg I/mL).

Small differences in visualization can affect your diagnosis. Select Isovue-370 as your visual aid.



Two images taken in the same pediatric patient, with Isovue-370 (left) and ioxaglate 320 (right). The same volume of media was used for each image. Angles: left anterior oblique 60° and caudo-cranial 28°.[1]

As with all injectable contrast agents, the possibility of severe reactions should be borne in mind, regardless of the patient's preexisting medical history.

Please see the brief summary of prescribing information on the following page.

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ISOVUE®-200 **ISOVUE®-300** **ISOVUE®-370**
Iopamidol Injection 41% **Iopamidol Injection 61%** **Iopamidol Injection 76%**

CONTRAINDICATIONS—None.

WARNINGS—Nonionic iodinated contrast media inhibit blood coagulation *in vitro*, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions, and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of *in vitro* clotting.

Use caution in patients with severely impaired renal function, combined renal and hepatic disease, or anuria, particularly when larger doses are administered. Radiopaque diagnostic contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. It has been speculated that the combination of the contrast agent and dehydration may be causative of anuria in myelomatous patients. This risk is not a contraindication; however, special precautions are required. Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when injected intravenously or intraarterially. Administration to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If the possible benefits outweigh the considered risks, the procedures may be performed; however, the amount of the medium injected should be kept to an absolute minimum. Assess blood pressure throughout the procedure and have measures for treatment of a hypertensive crisis available. Monitor such patients very closely. Use caution in patients with hyperthyroidism or with an autonomously functioning thyroid nodule because of risk of thyroid storm.

PRECAUTIONS: General—Diagnostic procedures should be carried out under the direction of personnel with the prerequisite training and a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, or for emergency treatment of severe reaction to the agent itself. After parenteral administration, competent personnel and emergency facilities should be available for at least 30 to 60 minutes since severe delayed reactions may occur. Preparatory dehydration is dangerous and may contribute to acute renal failure in susceptible patients. *Patients should be well hydrated prior to and following administration.* Reactions to the medium, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (see ADVERSE REACTIONS in the product package insert). Patients at increased risk include those with a history of a previous reaction to a contrast medium, a known sensitivity to iodine per se, and a known clinical hypersensitivity (bronchial asthma, hay fever, and food allergies). Pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. A thorough medical history with emphasis on allergy and hypersensitivity prior to the injection of any contrast medium may be more predictive and accurate than pretesting. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. General anesthesia may be indicated in some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in anesthetized patients, which may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia which can reduce cardiac output and increase the duration of exposure to the agent. Even though the osmolality is low compared to diatrizoate or iothalamate based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. Observe these patients for several hours following the procedure. In angiographic procedures, be aware of the possibility of dislodging plaques or damaging or perforating the vessel wall during catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are suggested.

The inhibitory effects of nonionic contrast media on mechanisms of hemostasis have been shown, in vitro, to be less than ionic contrast media at comparable concentrations. For this reason, standard angiographic procedures should always be followed: angiographic catheters should be flushed frequently, and prolonged contact of blood with contrast in syringes and catheters should be avoided. Perform *selective coronary arteriography* only in those in whom the expected benefits outweigh the procedural risk. The inherent risks of *angiocardiography* in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure. *Angiography* should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In addition to the general precautions previously described, special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system.

Extreme caution during injection of contrast media is necessary to avoid extravasation and fluoroscopy is recommended. This is especially important in patients with severe arterial or venous disease.

Drug Interactions—Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of intravascular agents should therefore be postponed in any patient with a known or suspected hepatic or biliary disorder who has recently received a cholecystographic contrast agent. Other drugs should not be admixed with iopamidol.

Drug/Laboratory Test Interactions—PBI and radioactive iodine uptake studies will not accurately reflect thyroid function for up to 16 days following administration, however T3 resin uptake and total or free thyroxine (T4) assays are not affected. Any test which might be affected by contrast media should be performed prior to administration of the contrast media.

Carcinogenesis, Mutagenesis, Impairment of Fertility—In animal reproduction studies performed on rats, intravenously administered iopamidol did not induce adverse effects on fertility or general reproductive performance. In studies to determine mutagenic activity, iopamidol did not cause any increase in mutation rates.

Pregnancy Category B—No teratogenic effects attributable to iopamidol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether iopamidol crosses the placental barrier or reaches fetal tissues. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Radiologic procedures involve a certain risk related to the exposure of the fetus to ionizing radiation.

Labor and Delivery—It is not known whether use during labor or delivery has immediate or delayed adverse effects on the labor, the delivery or the newborn.

Nursing Mothers—It is not known whether iopamidol is excreted in human milk. Use caution when contrast media are administered to nursing women because of potential adverse reactions; consideration should be given to temporarily discontinuing nursing.

Pediatric Use—Safety and effectiveness in children has been established in pediatric angiocardiography, computed tomography and excretory urography.

Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, cyanotic heart disease, congestive heart failure, a serum creatinine greater than 1.5 mg/dL or those less than 12 months of age.

ADVERSE REACTIONS—Usually mild to moderate, self-limited and transient. In angiocardiography (597 patients), the adverse reactions with an estimated incidence of one percent or higher are: hot flashes 3.4%; angina pectoris 3.0%; flushing 1.8%; bradycardia 1.3%; hypotension 1.0%; hives 1.0%. Intravascular injection is frequently associated with the sensation of warmth and pain, especially in peripheral arteriography and venography; pain and warmth are less frequent and less severe with ISOVUE (iopamidol injection) than with diatrizoate meglumine and diatrizoate sodium injection. The following table of incidence of reactions is based on clinical studies with ISOVUE in about 2191 patients.

Adverse Reactions
Estimated Overall Incidence

System	>1%	≤1%
Cardiovascular	none	tachycardia, hypotension, hypertension, myocardial ischemia, circulatory collapse, S-T segment depression, bigeminy, extrasystoles, ventricular fibrillation, angina pectoris, bradycardia, transient ischemic attack, thrombophlebitis
Nervous	pain (2.8%) burning sensation (1.4%)	vasovagal reaction, tingling in arms, grimace, faintness
Digestive	nausea (1.2%)	vomiting, anorexia
Respiratory	none	throat constriction, dyspnea, pulmonary edema
Skin and Appendages	none	rash, urticaria, pruritus, flushing
Body as a Whole	hot flashes (1.5%)	headache, fever, chills, excessive sweating, back spasm
Special Senses	warmth (1.1%)	taste alterations, warmth in throat/arms/chest, nasal congestion, visual disturbances
Urogenital	none	urinary retention

Regardless of the agent employed, overall estimated incidence of serious adverse reactions is higher with *coronary arteriography* than with other procedures. Cardiac decompensation, serious arrhythmias, or myocardial ischemia or infarction may occur during *coronary arteriography and left ventriculography*. Following coronary and ventricular injections, certain electrocardiographic changes (increased QTc, increased R-R, T-wave amplitude) and certain hemodynamic changes (decreased systolic pressure) occurred less frequently with ISOVUE (iopamidol injection) than with diatrizoate meglumine and diatrizoate sodium injection; increased LVEDP occurred less frequently after ventricular iopamidol injections. In *aortography*, the risks of procedures also include injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, accidental selective filling of the right renal artery during the translumbar procedure in the presence of preexisting renal disease, retroperitoneal hemorrhage from the translumbar approach, and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Adverse effects reported in literature include arrhythmia, arterial spasms, hematuria, periorbital edema, involuntary leg movement, malaise, and triggering of deglutition; some of these may be procedural. Other reactions due to procedural hazards include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests; and rarely arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest.

General Adverse Reactions To Contrast Media—Mild, moderate, and sometimes severe adverse reactions may occur associated with the procedure and/or the contrast media. Reactions known to occur with parenteral administration of iodinated ionic contrast media (see the listing below) are possible with a nonionic agent. Approximately 95 percent of adverse reactions accompanying the use of other water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe and life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred.

Reported incidences of death from the administration of other iodinated contrast media range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005 percent) patients.

In a prospective clinical study involving patients undergoing an intravenous procedure, approximately 170,000 patients received nonionic low osmolar contrast media, with the majority of these receiving iopamidol. The overall incidence of adverse reactions was approximately three in 100 patients. The incidence of severe reactions was approximately four in 10,000.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions. Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category. Experience with iopamidol suggests there is much less discomfort (e.g., pain and/or warmth) with peripheral arteriography. Fewer changes are noted in ventricular function after ventriculography and coronary arteriography.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of drug injected, the speed of injection, the mode of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that for the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations. Most adverse reactions to intravascular contrast agents appear within one to three minutes after the start of injection, but delayed reactions may occur (see PRECAUTIONS, General).

In addition to the adverse drug reactions reported for iopamidol, the following additional adverse reactions have been reported with the use of other intravascular contrast agents and are possible with the use of any water-soluble iodinated contrast agent:

Cardiovascular: vasodilation, cerebral hematomas, petechiae.
Nervous: paresthesia, dizziness, convulsions, paralysis, coma.
Respiratory: increased cough, asthma, laryngeal edema, pulmonary edema, bronchospasm, rhinitis.
Skin and Appendages: injection site pain usually due to extravasation and/or erythematous swelling, skin necrosis.
Urogenital: osmotic nephrosis of proximal tubular cells, renal failure, pain.
Special Senses: bilateral ocular irritation; lacrimation; conjunctival chemosis, infection, and conjunctivitis.

The following reactions may also occur; neutropenia, thrombophlebitis, flushing, pallor, weakness, severe retching and choking, wheezing, cramps, tremors, and sneezing.

Overdosage—Treatment of an overdose of an injectable radiopaque contrast medium is directed toward the support of all vital functions, and prompt institution of symptomatic therapy. Intravenous LD_{50} values (gI/kg) for iopamidol in animals: 21.8 (mice), 13.6 (rats), 9.6 (rabbits), 17.0 (dogs).

For full prescribing information consult package insert. (J3-652P)

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Effect on Global and Regional Left Ventricular Functions by Percutaneous Transluminal Coronary Angioplasty in the Chronic Stage After Myocardial Infarction

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Data are reported on 145 consecutive patients with prior myocardial infarction who had successful percutaneous transluminal coronary angioplasty (PTCA) of the infarct-related artery (5 ± 6 months after infarction), and left ventricular (LV) angiograms before PTCA and during follow-up (7 ± 4 months). There was a significant long-term improvement in LV function, ejection fraction increased from 60 ± 13% to 64 ± 13% ($p < 0.001$), and regional wall motion abnormalities decreased by 40%. Multivariate discriminant analysis identified reduced LV function and a high degree of stenosis before PTCA as predictors for improvement in LV function (ejection fraction <60%: ejection fraction from 48 ± 9% to 57 ± 14%, $p < 0.001$; and stenosis ≥90%: ejection fraction from 59 ± 15% to 66 ± 14%, $p = 0.003$). Restenosis ≥90% in patients with initial stenosis <90% decreased ejection fraction from 59 ± 16% to 51 ± 14% ($p < 0.05$). Other factors tested (treatment of infarction by thrombolysis, time between infarction and PTCA, and severity of angina pectoris) had no effect on long-term changes in LV function.

It is concluded that successful elective PTCA of a high-grade stenosis in an infarct-related artery may improve LV ejection fraction and regional wall motion abnormalities, especially in patients with impaired LV function.

(Am J Cardiol 1992;69:997-1002)

Revascularization by aortocoronary bypass surgery can improve chronic left ventricular (LV) dysfunction after myocardial infarction. This observation was first seen in the early years of bypass surgery,[1] was confirmed by intraoperative echocardiographic studies[2] and led to the concept of "hibernating myocardium"[3]: myocardial infarction may put some still viable myocardium in a stage of impaired function from which recovery is possible when perfusion becomes adequate again. Currently, percutaneous transluminal coronary angioplasty (PTCA) is available as another means of myocardial revascularization. Contrary to surgical revascularization, PTCA in patients with myocardial infarction was studied mainly in the setting of acute myocardial infarction with or without thrombolysis.[4-8] Only a few reports of rather small numbers of patients examined the impact of PTCA on LV function in the chronic stage after myocardial infarction.[9-12]

This study investigates factors influencing the effect of PTCA of the infarct-related artery late after acute infarction on long-term changes of global and regional LV functions.

METHODS

Study patients: The study population comprised 145 patients (113 men and 32 women, mean age 55 years, range 31 to 82). They were selected from a data base of 500 consecutive, prospectively entered patients, according to the following 2 criteria: (1) myocardial infarction and elective successful PTCA of the infarct-related artery at any time after the acute phase of myocardial infarction, and (2) quantitatively evaluable LV angiograms obtained before PTCA and during follow-up. Successful PTCA was defined as ≥20% reduction of percent diameter stenosis, and residual stenosis ≤50%. Restenosis was defined as >50% diameter stenosis at follow-up. 72 patients had anterior and 73 had inferior myocardial infarctions; 18 had another myocardial infarction before the qualifying one. During the same time, 76 patients without prior myocardial infarction had successful PTCA of ≥1 lesion, and an evaluable LV angiogram before PTCA and at follow up. These data were included for comparison.

Quantitative angiographic analysis: The technique for analyzing LV angiograms and coronary stenosis was described previously.[13] LV angiograms were obtained in the 30° right anterior oblique position. Ejection fraction was calculated according to the area-length method.

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TABLE I Results from the Multivariate Discriminant Analysis

Variable	Step	F Value	Wilks' Lambda	Canonical Discriminant Function Coefficient
EF before PTCA	1	15.9076	0.90450	0.86835
% stenosis before PTCA	2	5.5995	0.87019	−0.58537
% stenosis at follow-up	3	2.3677	0.85582	0.34828

EF = ejection fraction; PTCA = percutaneous transluminal coronary angioplasty.

Regional wall motion abnormalities were quantified as the regional dyssynergic area of the left ventricle by superimposing the end-diastolic and end-systolic contours using a fixed polar coordinate system, measuring the actual shortening of 48 radii, and calculating the area between the nominal value of shortening (2 standard deviations below the mean of healthy subjects) and the patients' actual radii shortening.

Coronary arteries were filmed in multiple projections, and stenoses were quantified by a computer-assisted caliper method. The edges of the normal as well as the stenotic segment of a vessel undergoing PTCA were marked by a cursor, and percent diameter stenosis was calculated as the mean value of multiple projections. Stenoses were measured before and immediately after PTCA, and during follow-up.

Tracing of LV contours and measurements of coronary artery stenoses were performed by clinicians not performing PTCA themselves, and in the case of the follow-up study, unaware of the baseline results.

Statistical analysis: Multivariate discriminant analysis was used to obtain factors influencing long-term improvement of LV function after PTCA. Patients with ejection fractions ≥5% higher at follow-up were considered as responders.[10,14] The following variables were entered in the analysis: baseline LV function (ejection fraction and regional dyssynergic area); initial degree of stenosis; degree of stenosis at follow-up; treatment of infarction (72 patients were treated by thrombolysis and 73 were not); time from infarction to PTCA (75 patients had PTCA ≤1 month after the acute event [mean 14 ± 8 days, range 1 to 29] and 70 patients >1 month [mean 38 ± 59 weeks, range 5 weeks to 7 years]); and degree of angina pectoris before PTCA (graded as proposed by the Canadian Cardiovascular Society).[15]

Multivariate discriminant analysis found (in the following order) a low ejection fraction, a high degree of stenosis before PTCA, and a low degree of stenosis at follow-up to be factors influencing long-term outcome. To dichotomize these continuous variables, we derived the threshold value for ejection fraction from univariate analysis (60%; mean ejection fraction [responder + nonresponder]/2). This approach was not usable for the subordinate factor degree of stenosis (before PTCA and at follow-up), because it was "overruled" by the ejection fraction. Dichotomization of these variables was data-derived, and the threshold value was set at 90% diameter stenosis. The analysis was additionally performed for these dichotomized threshold values and confirmed the validity of this approach.

Data are presented as mean ± standard deviation. The Statistical Package for the Social Sciences-X program was used for all statistical calculations. The paired *t* test was used for comparisons of data before PTCA and at follow-up, and the unpaired *t* test for comparisons among different groups. A p value <0.05 was considered significant.

RESULTS

All 145 patients with myocardial infarction had elective PTCA (mean 19 weeks after infarction). Mean time between PTCA and follow-up was 29 ± 18 weeks. Mean degree of percent diameter stenosis decreased from 79 ± 13% before to 27 ± 11% immediately after PTCA, and was 46 ± 29% at follow-up. Ejection fraction increased from 60 ± 13% to 64 ± 14% ($p < 0.001$) at follow-up, and the regional dyssynergic area decreased from 152 ± 177 to 92 ± 144 ($p < 0.001$). The number of akinetic radii in the infarcted region decreased in responders from 15.0 ± 9.7 to 7.2 ± 8.3 ($p < 0.001$). Baseline LV function was worse than in 70 patients without prior myocardial infarction undergoing PTCA during the study period and showed no significant changes after PTCA (ejection fraction from 69 ± 8% to 70 ± 9%, p = not significant [NS]; dyssynergic area from 31 ± 67 to 25 ± 63, p = NS).

Statistical analysis: The results of the multivariate discriminant analysis (Table I) showed that responders (patients with an improvement in ejection fraction of ≥5%) are characterized by a low ejection fraction before PTCA, a high degree of stenosis before PTCA, and a low degree of stenosis at follow-up. The major determinant was the baseline ejection fraction. It was detected in the first step of the analysis (Table I) and had the highest F value. The regional dyssynergic area was removed from further steps, because it provided the same information. If the baseline LV global and regional function is set aside, long-term outcome is influenced by the degree of stenosis before PTCA (second step, Table I) and finally by the degree of stenosis at follow-up (third step, Table I). Dichotomization of these continuous variables yielded a threshold value of 60% for ejection fraction, and ≥90% for degree of stenosis before PTCA or for restenosis at follow-up. Thus, ≥90% stenosis before PTCA characterizes the responders and at follow-up the nonresponders. Based on the 3 variables (baseline ejection fraction, and degree of stenosis before PTCA and at follow-up), 65% of all patients were classified correctly as either responders or nonresponders. All other variables entered into the analysis (see Methods and Table II) including clinical data before PTCA and at follow-up were discarded as having no independent effect on long-term changes in LV function. Furthermore, improvement in ejection fraction was independent of LV end-diastolic pressure, mean arterial pressure, heart rate, and withdrawal of β blockers between baseline and follow-up.

Subgroup analysis: The data of the various subgroups entered into and derived from the multivariate

TABLE II Left Ventricular Function Before Percutaneous Transluminal Coronary Angioplasty and at Follow-Up in Patients with Previous Myocardial Infarction

		Ejection Fraction			Dyssynergic Area			Ejection Fraction	
	No.	Baseline	Follow-Up	p Value	Baseline	Follow-Up	p Value	<60% at Baseline, No. (%)	Increase by ≥5%, No. (%)
Baseline EF									
<60%	60	48 ± 9	57 ± 14	<0.001	300 ± 176	168 ± 179	<0.001	—	39 (65)
≥60%	85	69 ± 6	69 ± 9	NS	47 ± 71	39 ± 78	NS	—	26 (31)
Baseline percent stenosis									
≥90%	32	59 ± 15	66 ± 14	0.003	170 ± 198	90 ± 151	0.003	16 (50)	21 (66)
<90%	113	61 ± 12	63 ± 12	0.005	146 ± 171	93 ± 142	<0.001	44 (39)	44 (39)
Stenosis at follow-up:									
No restenosis (≤50%)	94	60 ± 13	65 ± 12*	<0.001	139 ± 168*	80 ± 126*	<0.001	39 (41)	44 (47)
Restenosis >50–<90%	35	63 ± 11†	68 ± 11†	0.011	143 ± 185	68 ± 132†	0.007	11 (31)	15 (43)
Restenosis ≥90%	16	54 ± 15	52 ± 15	NS	245 ± 192	220 ± 201	NS	10 (63)	6 (38)
Treatment of infarction:									
No thrombolysis	73	58 ± 14	63 ± 13	<0.001	185 ± 192	109 ± 154	<0.001	36 (49)	35 (48)
Thrombolysis	72	62 ± 11	65 ± 13	NS	118 ± 154	75 ± 131	0.012	24 (33)	30 (42)
Time infarction to PTCA									
>1 month	70	57 ± 13‡	61 ± 13‡	0.002	193 ± 199‡	117 ± 157‡	<0.001	35 (50)	32 (46)
≤1 month	75	63 ± 11	66 ± 12	0.013	113 ± 145	69 ± 127	0.005	25 (33)	33 (44)
Angina pectoris									
0–1 CCS	40	62 ± 13	64 ± 13	NS	148 ± 183	96 ± 146	0.043	15 (38)	19 (48)
Stable	64	59 ± 14	63 ± 14	0.001	166 ± 175	100 ± 152	<0.001	30 (47)	31 (48)
Unstable	41	61 ± 11	65 ± 11	0.008	133 ± 175	76 ± 129	0.030	15 (36)	15 (36)

Significant ($p < 0.05$) differences among subgroups: *no restenosis versus restenosis ≥90%; †restenosis >50–<90 vs ≥90%; ‡≤1 vs >1 month.
CCS = Canadian Cardiovascular Society; NS = not significant; other abbreviations as in Table I.

analysis are summarized in Table II. There was a general trend toward improvement in all groups (except patients with severe restenosis), which was statistically significant in most cases.

LV function improved significantly in patients with a baseline ejection fraction <60%, and did not change in those with an ejection fraction ≥60% (Table II). Among patients with an ejection fraction <60%, 36 (60%) had no thrombolysis, and 35 (58%) had PTCA >1 month after infarction.

Patients with an initial ≥90% stenosis had much greater changes in ejection fraction than did those with <90% stenosis (7 vs 2%). Ejection fraction improved in two thirds of patients with ≥90% initial stenosis by ≥5% (Table II and Figure 1).

Patients without restenosis showed a significant improvement in LV function (Table II), whereas changes in ejection fraction were not significant in the 51 with restenosis (60 ± 13% before and 63 ± 15% after PTCA). Among patients with restenosis, LV function improved in those with <90% restenosis, but decreased in those with ≥90% restenosis (Table II).

A composite consideration of the degree of stenosis before PTCA and at follow-up provided the following results (Figure 2): LV function improved markedly in 19 patients with an initial ≥90% stenosis and no restenosis (ejection fraction 60 ± 15% to 69 ± 11%, p = 0.002; and dyssynergic area 142 ± 213 to 55 ± 155, p = 0.004), did not change in 13 with an initial ≥90% stenosis and restenosis (any degree) at follow-up (ejection fraction from 56 ± 15% to 61 ± 17%, p = NS; and dyssynergic area 211 ± 172 to 141 ± 186, p = NS) and deteriorated in 10 in whom the restenosis was worse (≥90) than the initial stenosis (>50 to <90%) (ejection fraction 59 ± 16 to 51 ± 14%, p = 0.05; and dyssynergic area 199 ± 231 to 236 ± 204, p = NS).

Among 51 patients with restenosis, 24 of 26 had successful repeat PTCA, 5 underwent bypass surgery, and

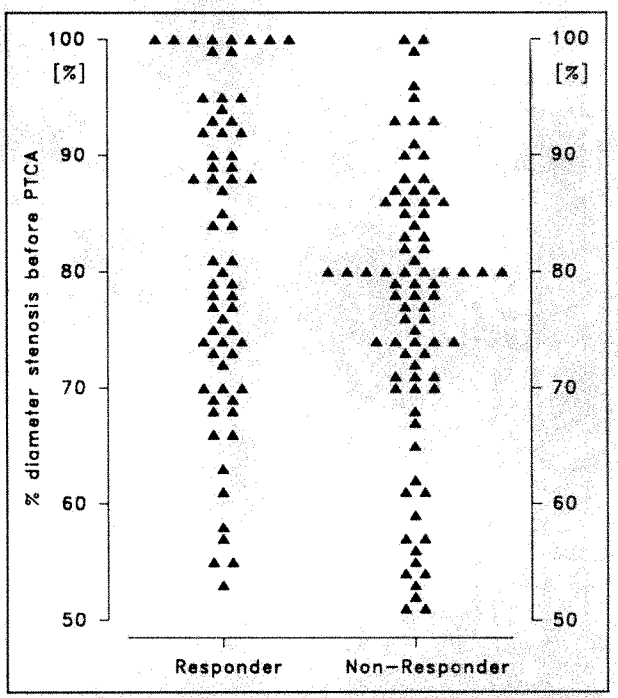


FIGURE 1. Frequency distribution of improvement in ejection fraction by ≥5% (responder) versus <5% (nonresponder) with regard to initial degree of stenosis. PTCA = percutaneous transluminal coronary angioplasty.

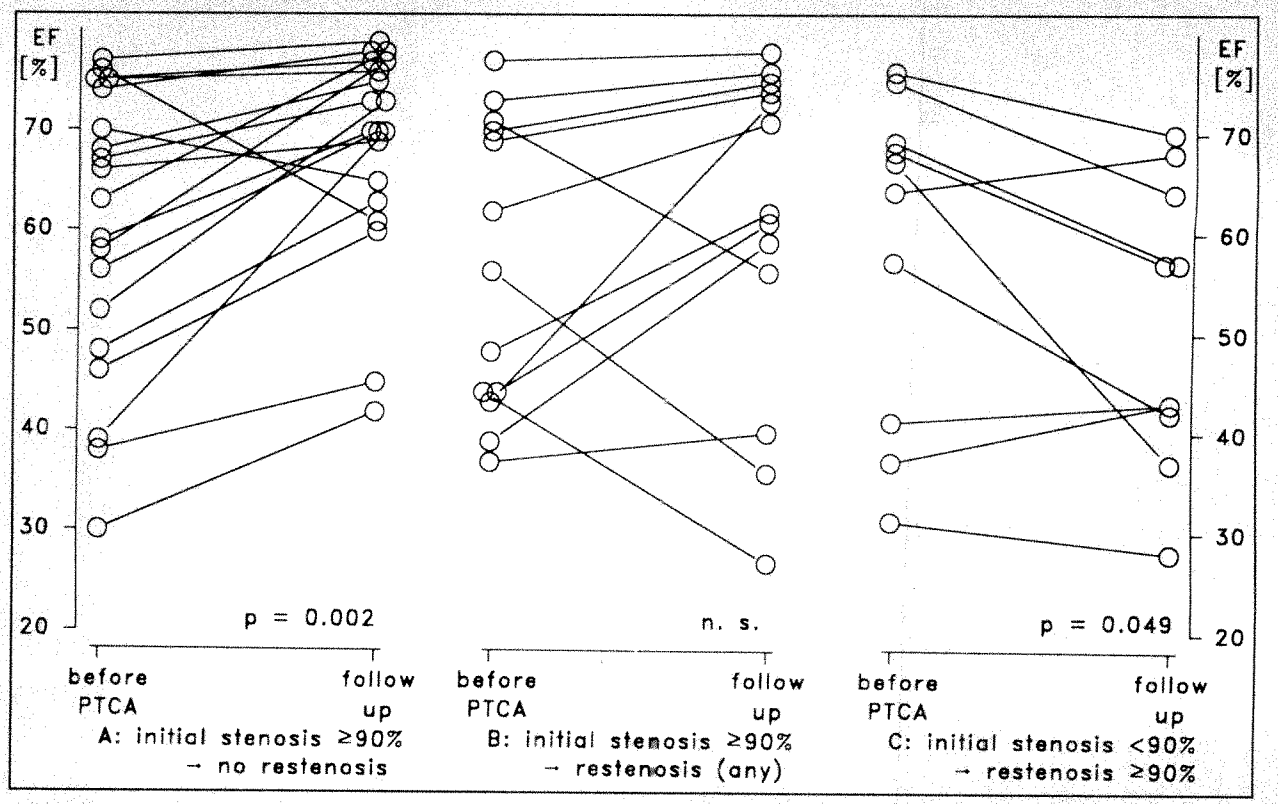


FIGURE 2. Changes of ejection fraction (EF) in patients with high-degree (≥90%) stenosis at baseline or follow-up. *A*, patients with initial stenosis ≥90% and no restenosis at follow-up. *B*, patients with initial stenosis ≥90% and restenosis (any degree) at follow-up. *C*, patients with initial stenosis <90% and severe restenosis (≥90%) at follow-up. n.s. = not significant; PTCA = percutaneous transluminal coronary angioplasty.

the remaining patients were treated medically because they were free of symptoms.

Thrombolytic therapy, time of infarction to PTCA, and degree of angina pectoris before PTCA and at follow-up are not independent factors in predicting outcome after PTCA. Improvement in LV function is dependent on baseline LV function and degree of stenosis. Changes in LV function are generally greater when baseline function is more reduced (Table II).

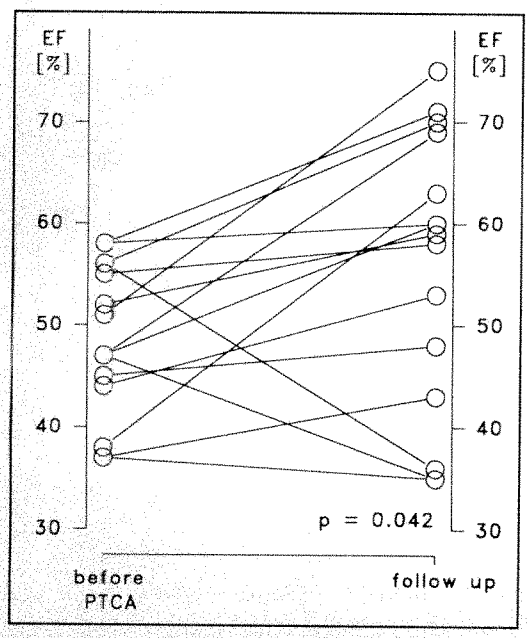


FIGURE 3. Changes of ejection fraction in patients with angina class 0–I and baseline ejection fraction <60%. Abbreviations as in Figure 2.

In the case of angina before PTCA there was a significant improvement in LV function in stable and unstable angina, but in patients without angina there was only a trend for ejection fraction to increase. Among these patients, 15 with a reduced baseline ejection fraction of <60% improved ejection fraction from 49 ± 7% to 56 ± 14% ($p = 0.042$) (Figure 3) and regional dyssynergic area from 322 ± 185 to 183 ± 164 ($p = 0.021$). In 2 patients in whom ejection fraction decreased markedly, the vessel was subtotally or totally occluded at follow-up.

DISCUSSION

During the past decade, PTCA became the treatment of choice for angina pectoris in 1-vessel disease. Our study indicates that PTCA late after an acute myocardial infarction may improve LV function similar to surgical revascularization.[1–3,14]

It has been shown in patients without prior myocardial infarction that PTCA reduces exercise-induced ischemic LV dysfunction[16–19] and does not change normal LV function at rest (as in our control group),[16–18] whereas impaired LV function may improve.[10,19,20] In patients with prior myocardial infarction, acute and long-term improvement of a reduced LV function has been reported in a small number of patients.[9–12]

Elective percutaneous transluminal coronary angioplasty after infarction: Statistical analysis showed that the major determinants for long-term improvement in LV function were an impaired LV function before PTCA, followed by degree of stenosis of the infarct-related artery before PTCA and at follow-up. All clinical variables examined (including the various degrees of angina) had no effect on long-term outcome by themselves. This means, for instance, that differences in long-term outcome between patients with and without thrombolysis are not related to the different therapeutic regimens, but are due to a better preserved LV function in those treated by thrombolysis. The same is true for time between infarction and PTCA, and also for the various degrees of angina.

In a comparative study of acute changes in LV function after PTCA in stable versus unstable angina, PTCA normalized only the reduced LV function at rest in unstable angina, whereas the normal function in stable angina was not altered.[21] We also included patients with functional class 0–1. Although ejection fraction did not change significantly in this group, these patients benefited also from PTCA if baseline LV function was impaired (Figure 3). Surgical revascularization also improved LV function in patients with chronic coronary artery disease without angina pectoris, but with impaired LV function.[22] However, the usefulness of PTCA for asymptomatic patients needs to be clarified.

PTCA implies the problem of restenosis. There are few data on the impact of restenosis on LV function. The reappearance of previously abolished wall motion abnormalities[16] has been noted, as well as improvement in LV function with restenosis, and no change with reocclusion.[9]

The overall nonsignificant change of ejection fraction in restenosis characterizes the problem of restenosis insufficiently. LV function may improve in cases with a moderate (<90%) restenosis, but decrease with a high-degree (≥90%) one, especially if the restenosis is worse than the initial stenosis (Table II and Figure 2). Furthermore, patients with an initial ≥90% stenosis but no restenosis had the largest improvement in LV function, whereas the changes varied in those with moderate restenosis (Figure 2).

Hibernating myocardium: The amount of myocardial damage after infarction (presenting as asynergy in the LV angiogram) varies depending on duration of ischemia, residual anterograde perfusion through the culprit lesion, and collateral support. It ranges between "stunned" (delayed recovery after spontaneous restoration of blood flow), "hibernating" (recovery needs revascularization) and "embalmed" (irreversibly dead) myocardium.[3,23] Recovery of impaired LV function after reperfusion of a totally occluded (10 of 13 patients are responders; Figure 1) or highly stenotic infarct-related artery fits the concept of hibernating myocardium.[3]

Study limitations: This study and others attribute the observed improvement in LV function after PTCA to the procedure itself. However, improvement in LV function after acute myocardial infarction also occurs spontaneously, but mainly in the first days,[24,25] and long-term improvement occurs in those with a low-grade stenosis.[13] In our study improvement by PTCA was observed in the "opposite" groups (i.e., late after infarction and in high-grade stenosis). Furthermore, in unsuccessful PTCA, absence of LV improvement has been reported.[11] Thus, spontaneous changes were probably of minor importance, but final proof needs controlled studies.

Clinical implications: Improvement in impaired LV function after myocardial infarction by PTCA of an infarct-related artery late after the event may have some impact on future treatment of patients after infarction. However, the risks of PTCA should be considered. The predictive accuracy (65%) of the angiographic factors found (baseline LV function and degree of stenosis) may be improved by provocative measures to identify viable myocardium before intervention. Thus, prospective controlled studies are needed (especially concerning preintervention identification of responders in terms of improvement in LV function) before therapeutic recommendations can be made.

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Circadian Distribution of Onset of Acute Myocardial Infarction in Subgroups from Analysis of 10,791 Patients Treated in a Single Center

Ole Hansen, MD, PhD, Bengt W. Johansson, MD, PhD, and Bo Gullberg, PhD

A circadian variation of symptom onset in acute myocardial infarction (AMI) with an increased frequency in the late morning and possibly also in the evening has been found in several studies. It has been suggested that different circadian rhythms may exist in various subgroups of patients. This possibility was examined in a population of 10,791 patients collected between 1973 and 1987 in a continuously operating register of patients with AMI in Malmö, Sweden. In 6,763 patients (63%) in whom a distinct symptom onset could be established, symptom onset occurred with an increased frequency between 6:01 A.M. and 12:00 noon (30.6%) and between 6:01 P.M. and 12:00 midnight (26.9%). Similar bimodal circadian rhythms were seen in patients aged >70 years (n = 2,923), ≤70 years (n = 3,840), men (n = 4,528), women (n = 2,235), smokers (n = 2,458), hypertensives (n = 1,999), diabetics (n = 653), patients with (n = 1,872) and without (n = 4,891) a history of previous AMI, and in patients with recent non-Q-wave AMI (n = 333). In 455 patients receiving cardioselective β blockers the circadian distribution did not differ from a random, whereas in patients taking nonselective β blockers or calcium antagonists significant bimodal rhythms were found. Statistically significant interactions were found between symptom onset and age dichotomized at 70 years, and between patients with and without a history of previous AMI. In a multivariate analysis only these variables (age ≤/>70 years; ± history of a previous AMI) were found to modify the circadian rhythm of symptom onset in the population.

It is suggested that only minor differences in symptom onset between various subgroups exist within the same population, and that these differences probably are unable to explain differences in circadian rhythm of symptom onset between different populations.

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A circadian variation of the onset of acute myocardial infarction (AMI) with an increased incidence between 6:00 A.M. and noon has repeatedly been reported in several publications during the last decades.[1–7] In some studies a secondary peak in the frequency of onset of AMI has been recognized in the late evening.[1,2,4,5,7] The circadian variation is recognizable when the assessment of onset is based on patient reporting of symptoms or on objective measures including serial analyses of creatine kinase. An excellent correlation between symptom defined and enzymatically assessed AMI onset has been demonstrated,[4,6] although the use of creatine kinase determinations seems to augment the circadian variation of AMI onset within a population.[4] Circadian distributions similar to that of AMI onset have been recognized also for deaths from hospitalized AMI,[7] and for other clinical manifestations of coronary artery disease such as sudden cardiac death,[8] symptomatic or asymptomatic transient myocardial ischemia[9,10] and ventricular tachycardia.[11] Some studies have suggested that the circadian rhythm of AMI onset may be modified by several factors,[4–6] but because the studies reported retrospective subgroup analyses based on relatively small samples of patients, their results may need confirmation by further studies. Malmö, the third largest city in Sweden with a stable and defined population of approximately a quarter of a million is unusually well-suited for epidemiologic studies,[12] since the whole population is served by only 1 hospital for acute diseases. The present report is based on data collected in a register of AMI, which has been continuously operating in Malmö since 1972, and attempts to analyze the circadian distribution of AMI onset in different subgroups of patients already described in previous reports in order to confirm their findings, and examine if the circadian rhythm of AMI onset within a population is modified by different circadian patterns in various subgroups.

METHODS

The study is based on the discharge register in the department of medicine. All medical records of patients living in Malmö with a discharge diagnosis of verified or suspected AMI have been reviewed. Patients who died in the emergency room are included in the register, but not those dead on arrival. Only medical records fulfilling the following criteria for AMI have been included in the register: (1) central chest pain, lung edema, syncope or shock; (2) appearance of a pathologic Q wave in ≥2 leads, or (non-Q-wave AMI) appearance or reversion of ST-segment elevation followed by T-wave

TABLE I Characteristics of Study Population and Patients Without Defined Symptom Onset

Variable	Study Population (n = 6,763)	Patients Without Defined Symptom Onset (n = 4,028)
Age (mean ± SD)	67.9 ± 10.9	71.6 ± 10.8
Men	4,528 (67.0%)	2,369 (58.9%)
Women	2,235 (33.0%)	1,659 (41.1%)
Smokers	2,458 (36.3%)	739 (18.3%)
History of hypertension	1,999 (29.6%)	994 (24.7%)
Diabetes mellitus	653 (9.7%)	419 (10.4%)
Previous AMI	1,872 (27.7%)	1,003 (24.9%)
Nonselective β blocker*	553 (8.2%)	256 (6.4%)
Selective β blocker*	455 (6.7%)	265 (6.6%)
Calcium antagonist*	446 (6.6%)	319 (7.9%)
Present non-Q-wave AMI	333 (4.9%)	275 (6.8%)

*Treatment on admission.
AMI = acute myocardial infarction.

inversion (12-lead serial electrocardiograms); (3) 2 aspartate aminotransferase (ASAT) values greater than the laboratory's upper reference value (maximum appearing approximately 24 hours after the onset of symptoms) combined with increased alanine aminotransferase values (maximum approximately 36 hours after onset of symptoms and lower than the ASAT values), or 2 lactate dehydrogenase values greater than the laboratory's upper reference value (maximum of approximately 60 hours after onset of symptoms and with an increase of isoenzymes I and II); or 1 elevated ASAT and 1 elevated lactate dehydrogenase value; (4) autopsy confirming a diagnosis of myocardial infarction.

Myocardial infarction at autopsy or ≥2 of criteria 1 to 3 were required for a diagnosis of myocardial infarction. The diagnosis of a non-Q-wave AMI required a typical electrocardiographic evolution as described previously combined with both criteria 1 and 3. The classification of a myocardial infarction as a first-time infarction was based on the patient's history and previous records. Reinfarctions within 28 days after first admission were not included as new cases. The medical records were examined by specially trained staff. All doubtful records were judged by a cardiologist. The validity of the case selection was checked continuously by a cardiologist by examination of randomly selected samples of included cases. The years 1973 to 1987 yielded 10,791 infarctions — 6,897 in men and 3,894 in women.

Patients in whom a reliable symptom onset could not be defined either because they had experienced recurrent episodes of chest pain before admission or because AMI remained undiagnosed until autopsy, and those in whom symptom onset was not precisely stated in the files, were excluded from the present study; this left a study population of 6,763 patients (63%). Characteristics of the study population and the excluded patients are listed in Table I.

Definition of subgroups: The continuous registration of AMI in the AMI register includes the collection of data relating to the patient's social status, employment, prior medical history, current medication, and the clinical course during the hospital stay. Before the analysis was performed, the following subgroups were defined: (1) patients >70 years; (2) patients ≤70 years; (3) men; (4) women; (5) active smokers at the time of AMI; (6) patients with former or current treatment of hypertension, even without information on blood pressure level; (7) patients with a diagnosis of diabetes mellitus irrespective of insulin dependency; (8) previous AMI according to history or prior medical records; (9) no previous AMI according to medical history or previous medical records; (10) current treatment with nonselective β blockers; (11) current treatment with selective β blockers; (12) current treatment with calcium antagonists; and (13) present non-Q-wave AMI.

Time of symptom onset: In all patients included in the study, the onset of AMI symptoms was stated in the files in 30-minute intervals. For calculations, the frequency of onset was tabulated for each hour in the day, beginning 1 minute after the previous hour. Furthermore, the day was divided in four 6-hour periods as follows: 12:01 A.M. to 6:00 A.M., 6:01 A.M. to 12:00 noon, 12:01 P.M. to 6:00 P.M., and 6:01 P.M. to 24:00 midnight.

Statistical analysis: The circadian distributions of symptom onset in the entire study population and in the various subgroups were tested for uniformity by a chi-square test for goodness of fit. Uniformity was evaluated by each hour, and within the four 6-hour periods. A peak in symptom onset was considered present if the percentage of onset within a 6-hour period exceeded 25% of all AMIs in the same subgroup and if uniformity could be rejected. In addition, a chi-square test based on a 2 by 4 contingency table, including the four 6-hour interval and the subgroups with and without the variable defining the subgroups, was performed in order to detect a possible interaction between AMI onset and the various subgroups. Finally, a multivariate analysis (polychotomous stepwise logistic regression) was used to evaluate if any of the variables used to define the various subgroups modified the circadian rhythm of symptom onset within the entire population.

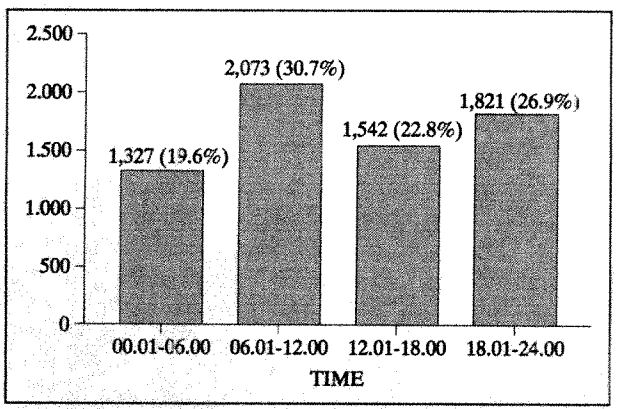


FIGURE 1. The circadian distribution of symptom onset in 6,763 patients.

RESULTS

The circadian distribution of symptom onset in the entire study population is shown in Figure 1 (each hour) and Figure 2 (6-hour periods). A major peak between

TABLE II Percentages of Patients in the Subgroups in the Four 6-Hour Periods of Symptom Onset

Subgroup	Time Period				p Value*
	12:01–6:00 A.M.	6:01–12:00 Noon	12:01–6:00 P.M.	6:01–12:00 MN	
All (n = 6,763)	19.6	30.7	22.8	26.9	<0.001
Age > 70 years (n = 2,923)	19.8	31.1	20.9	28.2	<0.001
Age ≤ 70 years (n = 3,840)	19.5	30.3	24.3	25.9	<0.001
Men (n = 4,528)	19.9	30.1	23.5	26.4	<0.001
Women (n = 2,235)	19.0	31.7	21.4	28.0	<0.001
Smokers (n = 2,458)	20.3	29.2	23.6	26.9	<0.001
History of hypertension (n = 1,999)	20.5	30.8	22.0	26.8	<0.001
Diabetes mellitus (n = 653)	20.7	28.2	22.1	29.1	<0.01
Previous AMI (n = 1,872)	19.5	28.6	22.7	29.2	<0.001
No previous AMI (n = 4,891)	19.7	31.4	22.8	26.1	<0.001
Nonselective β blockers (n = 553)†	20.4	28.6	21.9	29.1	<0.001
Selective β blockers (n = 455)†	21.1	25.9	25.1	27.9	0.215
Calcium antagonists (n = 446)†	20.9	31.2	20.2	27.8	<0.01
Present non-Q-wave AMI (n = 333)	18.6	29.1	24.0	28.2	<0.05

*Test of uniformity.
†Treatment on admission.
AMI = acute myocardial infarction; MN = midnight.

7:01 A.M. and 11:00 noon, and 2 minor peaks, 15:01 P.M. to 16:00 P.M. and 9:01 P.M. to 10:00 P.M. can be identified. According to the statistical test of uniformity the circadian distribution differed significantly ($p < 0.001$) from random. When symptom onset was computed by the four 6-hour periods, 2 peaks were identified, 1 between 6:01 A.M. and 12:00 noon (30.7% of all AMIs), and 1 between 6:01 P.M. and 12:00 midnight (26.9% of all AMIs).

In Table II the symptom onset within the 6-hour periods is shown for the various subgroups. In all groups, 2 peaks each comprising >25% of all AMIs within the subgroup could be recognized in the late morning and in the evening, respectively. In all subgroups, except in patients receiving treatment with a selective β blocker at the time of their AMI, uniformity could be rejected, indicating that a significant circadian rhythm was present.

In patients aged >70 years, a significantly accentuated evening peak was found compared with patients ≤70 years ($p = 0.007$, test of independence), suggesting an interaction between symptom onset and age. An accentuated evening peak was found also in patients with a history of previous AMI compared with patients with no history of previous AMI ($p = 0.033$, test of independence). No significant interaction was found between symptom onset and treatment with a selective β blocker ($p = 0.148$, test of independence), or with any of the other variables defining the subgroups.

The multivariate analysis performed in order to identify modifying factors of symptom onset confirmed that age dichotomized by 70 years ($p = 0.007$) and a history of previous AMI ($p = 0.035$) significantly modified the circadian distribution of symptom onset within the entire population, whereas the effect of treatment with a selective β blocker did not reach traditional levels of statistical significance ($p = 0.20$). The other studied potentially modifying variables as defined by the subgroups were without significant effect on onset of symptoms.

DISCUSSION

In all subgroups in the present study, except in patients taking selective β blockers, statistically significant bimodal circadian rhythms were found. This was in contrast to previous reports, which claimed that in addition to treatment with β blockers the circadian pattern of AMI onset may be modified by age, gender, a history of hypertension and a history of prior AMI.[5] The influence of treatment with β blockers was studied by Willich et al,[6] who found that the morning peak was absent in patients receiving treatment with β blockers before their AMI. In the study by Muller et al[4] the morning peak was also absent in patients taking β blockers, but the subgroup was small (135 patients) and subsequently the statistical power to detect a real difference was moderate (48%). Hjalmarson et al[5] reported minor peaks in the late morning and in the evening in patients taking β blockers, but according to the statistical test of uniformity applied by them, the circadian rhythm was not significant. Thus, current treatment with β blockers at the time of AMI onset is associated with a diminished morning peak, but no previous study has considered the possibility of differences between cardioselective and

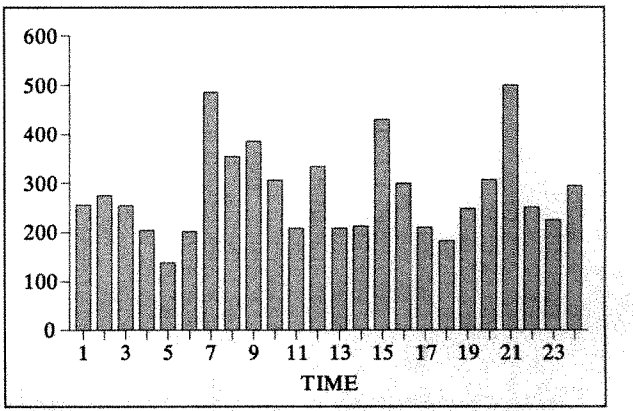


FIGURE 2. The circadian distribution of symptom onset in 6,763 patients (6-hour periods).

nonselective β blockers in that respect. The large number of patients in the present study allowed us to analyze the circadian distribution of AMI onset separately in patients receiving cardioselective and nonselective β blockers without the loss of an adequate statistical power; we found a statistically significant 2 peak distribution in patients taking a nonselective β blocker, whereas in patients treated with a cardioselective β blocker AMI onset did not differ significantly from random.

A lack of circadian variation at onset has been reported for non-Q-wave AMI in the Diltiazem Reinfarction Study,[13] but in the study by Hjalmarson et al[5] a peak was seen in the evening. In the present study we recognized both a morning and evening peak, and we were unable to find any significant interaction between the 6-hour intervals of AMI onset and patients with and without present non-Q-wave AMI. Part of the discrepancy in the findings can be explained by differences in the definition of a non-Q-wave AMI; many small non-Q-wave AMIs that would have been detected had we included creatine kinase in our diagnostic criteria may have been classified as angina pectoris in this study. The fact that only 4.9% of all AMIs in our study were classified as non-Q-wave AMI in contrast to 20% in the study by Hjalmarson et al[5] and 40% in the study by Muller et al[4] supports our belief that major differences in case ascertainment exist between the studies.

We believe it is reasonable to interpret the results of subgroup analyses of AMI onset with at least the same caution as that used when the results of subgroup analyses in clinical trials are interpreted.[14] This is especially true when remarkable results are found in some subgroups. In most of our subgroups a circadian rhythm similar to that seen in the whole study population was found; this was not seen in the study by Hjalmarson et al.[5] The different results of the 2 studies may partly be due to differences in the definition of subgroups and the limitations of subgroup analyses previously discussed. However, these discrepancies might possibly be due to the selection of the study populations. In the study by Hjalmarson et al, the study population was recruited from 6 different centers on 2 continents. The contribution from each center differed considerably. Patients were excluded if they failed to sign an informed consent, or were in need of coronary bypass surgery within the first week. In the present study we included patients collected in an AMI register continuously operating since 1972. These patients are representative of all hospitalized AMI patients in a community with only 1 hospital serving a stable and defined population of approximately 230,000 inhabitants. We had to exclude a substantial part of the patients in whom the symptom onset could not be exactly assessed. A major portion of these patients had experienced recurrent episodes of chest pain before admission, and in that way they differed from the study population. The excluded patients also had a higher in-hospital case fatality. This higher case fatality may be due to selection mechanisms, since most of the deaths could have occurred soon after admission and before a proper medical history with distinct information of symptom onset was obtainable. Furthermore, patients in whom AMI remained undiagnosed until autopsy were excluded.

The reason(s) for the circadian distributions of manifestations of coronary heart disease is not satisfactorily established, but it has been suggested that the morning peak may be causally related to other known physiologic circadian rhythms. The morning hours are characterized by an increase in the activity of the sympathetic nervous system, and an increased, although decreasing, cortisol secretion. Although the circadian rhythm of cortisol secretion seems independent of daily activity, the increase in sympathetic activity may possibly be related to the rest-activity cycle; it has been shown that after adjustment for time of awakening, infarct onset[15] and episodes of transient myocardial ischemia[9] follow awakening. The increased sympathetic activity after awakening results in increased levels of circulating adrenaline, with increases in heart rate, blood pressure[16] and coronary vascular tone, which may not only shift the relation between myocardial oxygen demand and oxygen supply in a disadvantageous way, but also facilitate rupture of coronary arteriosclerotic plaque and initiate thrombus formation. Furthermore, thrombus formation or propagation may occur more easily during the morning hours because fibrinolytic activity is low (although increasing) and platelet aggregability increases after awakening and assuming the upright position.[17]

In the present study the morning increase in AMI onset was blunted only in patients taking cardioselective but not nonselective β blockers. If this striking difference between the 2 subgroups is true, one can speculate whether the difference is due to differences in the β blockade, per se, or to other differences between patients. In the multivariate analysis we found age dichotomized at 70 years and a history of previous AMI as the only significant modifiers of AMI onset. There were no significant differences between the patients receiving cardioselective and nonselective β blockers with respect to these 2 modifiers of AMI onset, which might suggest a difference between cardioselective and nonselective β blockers in their ability to prevent morning increase in AMI onset. Although the postulated difference between cardioselective and nonselective β blockers should be confirmed by other studies, one might speculate at the possible reasons for such a difference: Known differences in the actions of cardioselective and nonselective β blockers in situations with increased circulating adrenaline should be considered. In healthy volunteers infused with adrenaline at a rate to achieve serum concentrations comparable to those seen in patients with AMI, pretreatment with a nonselective but not a cardioselective β blocker resulted in an increase in diastolic blood pressure, probably due to an unopposed α receptor-mediated vasoconstriction.[18] This pressor effect of nonselective β blockade has been observed not only in healthy volunteers, but also in hypertensive patients during ordinary environmental stress[19]; such stress probably increases the myocardial oxygen demand, compared with the situation with cardioselective β blockade. Also, it has been suggested that the nonselective β blocker pro-

pranolol may potentiate coronary vasoconstriction in patients with coronary artery disease during cold pressor testing.[20] The importance of the increase in myocardial oxygen demand or decrease in oxygen supply in the late morning, probably secondary to increased sympathetic activity, is emphasized by the observation that the number of angina attacks in patients with stable angina and the number of symptomatic or asymptomatic episodes of myocardial ischemia also peak in the late morning, coincident with the peak period of AMI onset.[9,10] It appears that the increase in myocardial oxygen demand is of greater importance than the increase in platelet aggregability during the morning increase in myocardial ischemia (the cardioselective β blocker metoprolol may reduce the frequency of transient ischemic events in the morning hours[21,22] without affecting the concomitant increase in platelet aggregability[22]). Moreover, the cardioselective β blocker atenolol has been shown to reduce both total number and duration of asymptomatic and symptomatic ischemic episodes in patients with angina,[23] whereas in the study by Taylor et al[24] treatment with β blockers (no distinction between cardioselective and nonselective was done) was not associated with a changed circadian rhythm of angina attacks compared with such attacks in patients taking no β blockers.

It is probable that platelet aggregability may be of greater importance during the morning increase in AMI incidence, because the presence of an occlusive thrombus is a frequent finding in AMI. However, although the platelet aggregation inhibitor aspirin may prevent AMI,[25,26] its potential in blunting the morning increase in AMI needs further confirmation. In the Physicians' Health Study, no circadian rhythm in AMI onset was seen in a subset of 75 patients taking aspirin at the time of their AMI.[27] The greatest reduction in AMI incidence attributable to aspirin was found between 4 A.M. and 10 A.M., but even in a 1-tailed statistical test, this reduction was not significantly different from the mean reduction seen in other periods of the day.

The reasons for the evening peak in AMI onset are not clear, but because approximately 70% of all AMIs occur at other times of the day than the late morning, it is probable that AMI triggering factors, related or unrelated to the physiologic parameters already discussed, exert their effects through all hours of the day.[28] Recently, Muller et al[29] summarized several potentially triggering daily activities, and have advanced the hypothesis that the evening peak may represent a synchronization of the population for an additional trigger such as the evening meal. In addition, it has been reported that the assumption of the supine position with elevation of cardiac filling pressure is associated with nocturnal ischemia,[30] and in this connection it is interesting that Hjalmarson et al[5] found a prominent evening peak in AMI onset in patients with a history of congestive heart failure. One can speculate whether such a mechanism is partially responsible for the significantly accentuated evening peak seen in the present study in patients older than age 70 years, and in patients with a history of previous AMI, since these patients are probably more apt to have congestive heart failure than patients from the complementary subgroups.

In summary, our study suggests that different circadian patterns of AMI onset in various subgroups of patients may modify the circadian rhythm of AMI onset within a population, but the differences in AMI onset between subgroups of patients might be less than previously anticipated, and might explain only a minor part of the difference in circadian rhythm of AMI onset between different populations; thus, factors influencing the selection of the study population may be of importance.

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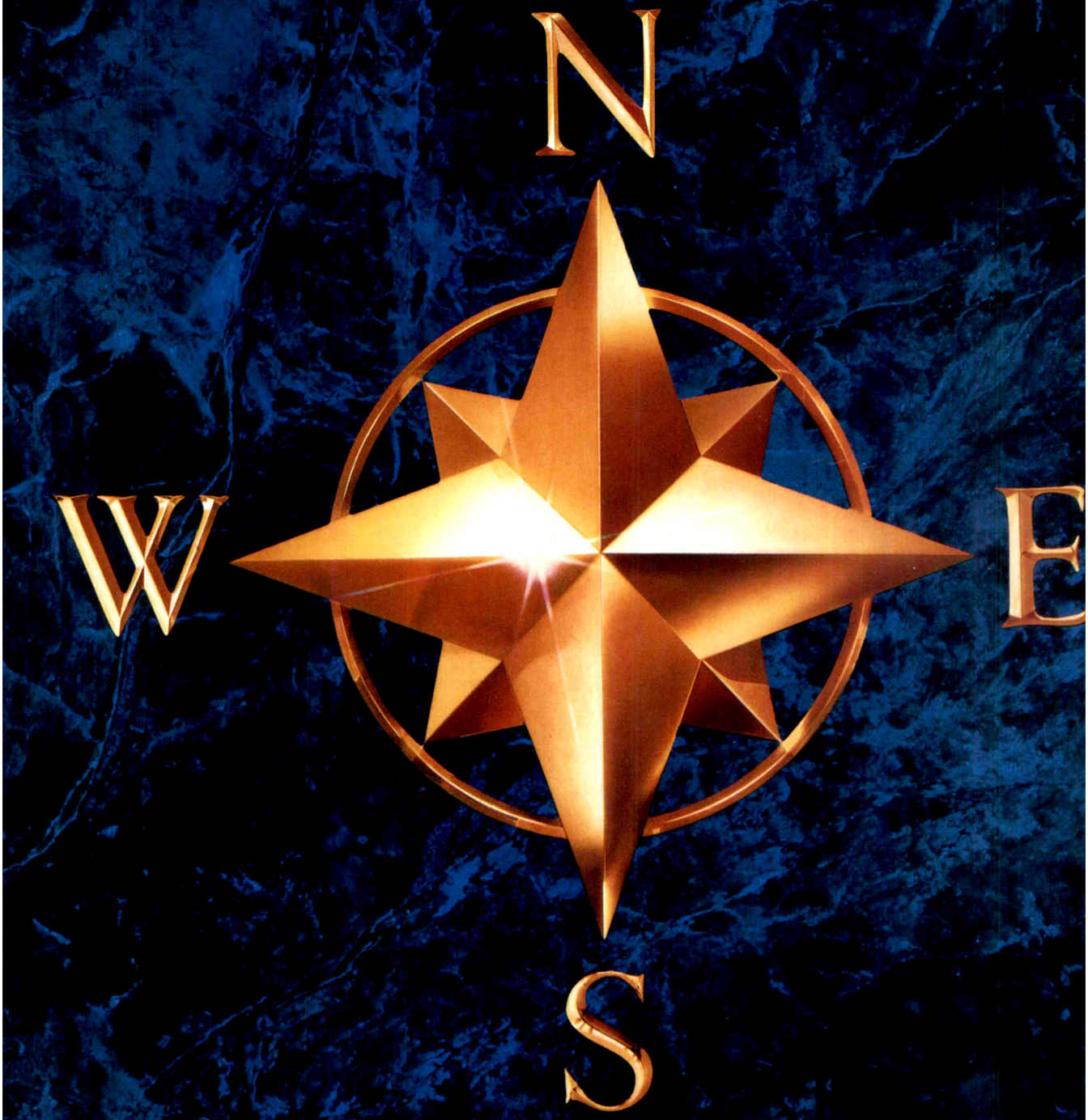
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BRISTOL-MYERS SQUIBB INTRODUCES

A NEW DIRECTION IN LIPID MANAGEMENT



A NEW DIRECTION IN LIPID MANAGEMEN

New



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PRAVACHOL™

pravastatin sodium 20 mg tablets

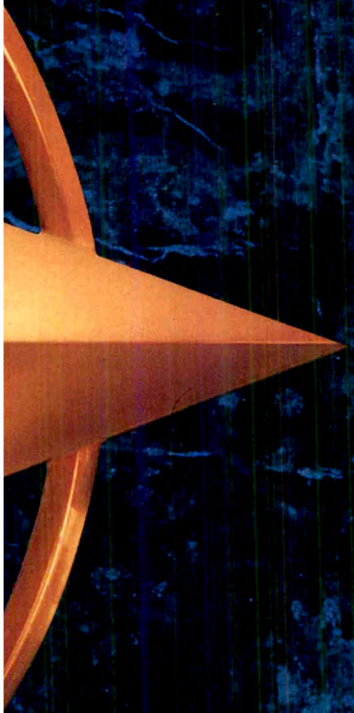
distinct new option
cholesterol management
or primary hypercholesterolemia
when diet alone is inadequate

- Consistently and significantly reduces total C and LDL-C
- Positively affects other key lipids
- Excellent safety and tolerability profile
- True once-a-day dosing with or without food
- Prescribed for more than 1,000,000 patients worldwide[1]
- Studied in over 13,000 patients worldwide in clinical research[1]
- New hydrophilic structure; the clinical effect of hydrophilicity, if any, has not been established
- Administered in the active form

PRAVACHOL® is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

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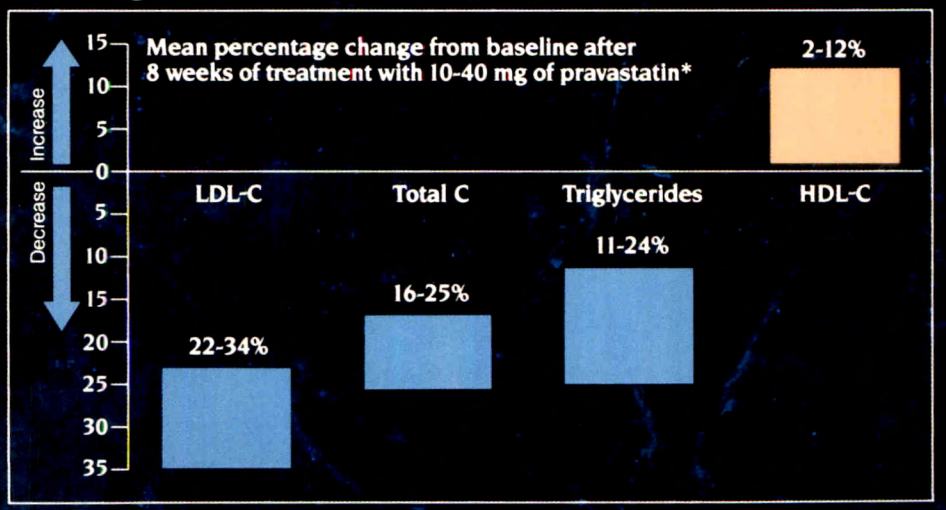
A NEW DIRECTION IN LIPID MANAGEMEN



Effective cholesterol control

PRAVACHOL® is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Consistently and significantly reduces atherogenic LDL-C. Increases beneficial HDL-C.[2]



*Each bar represents a range of means derived from a single placebo-controlled study that included 55 patients treated with pravastatin.

Pharmacology and metabolism

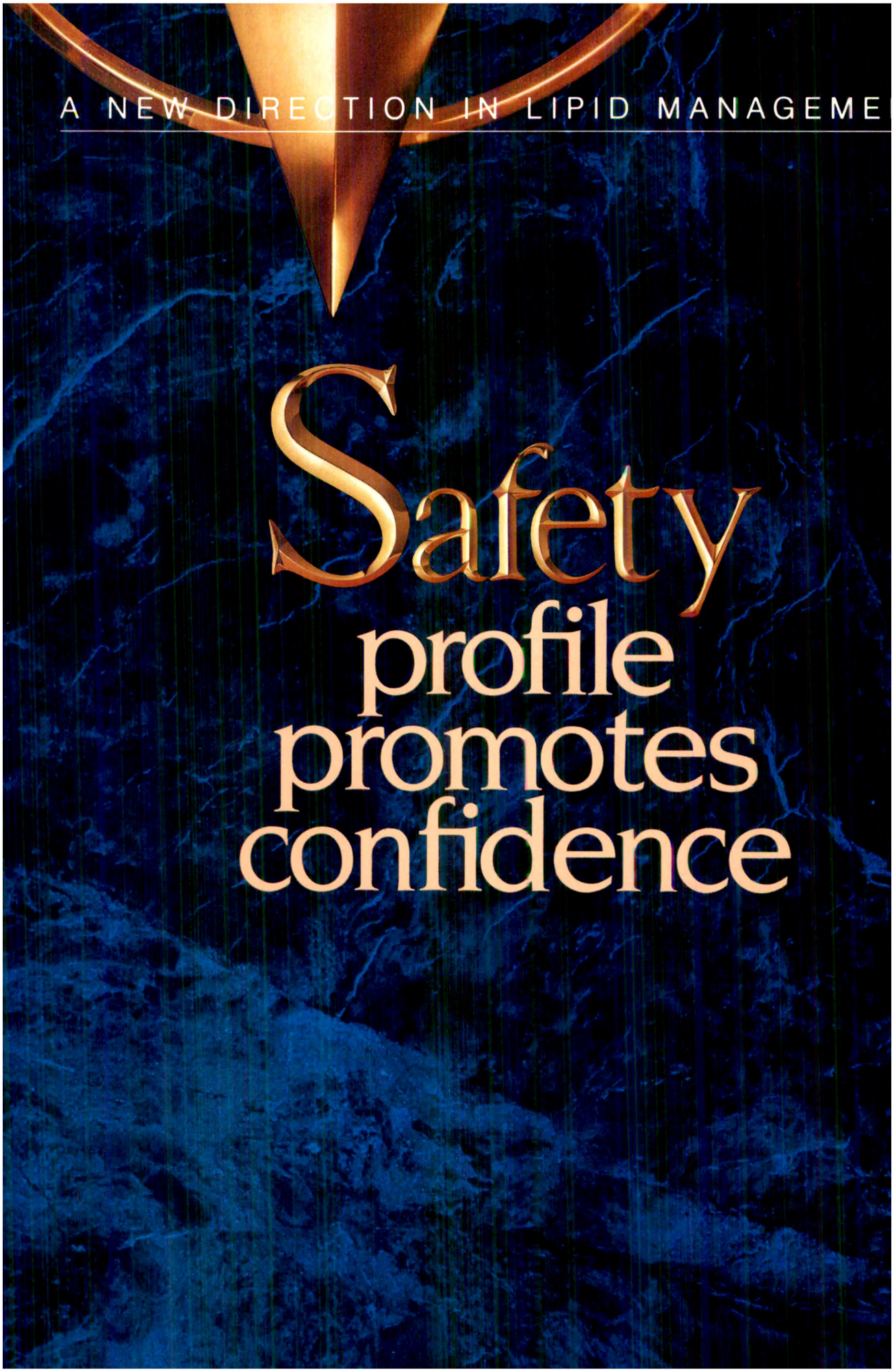
- PRAVACHOL® is administered in the active form
- PRAVACHOL is hydrophilic; the clinical effect of hydrophilicity, if any, has not been established
- PRAVACHOL is selective to the primary site of cholesterol synthesis, the liver
- *In vitro* studies demonstrated that pravastatin is transported into hepatocytes with substantially less uptake into other cells

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PRAVACHOL™

pravastatin sodium 20 mg tablets

A new direction in lipid management


A NEW DIRECTION IN LIPID MANAGEME
Safety
profile
promotes
confidence

Possibly associated myopathy in only 1 patient in clinical trials (n>13,000)*[1]

Consider myopathy in any patient with diffuse muscle pain, tenderness, or weakness, particularly with malaise or fever. Advise patients to promptly report these symptoms. Discontinue pravastatin if myopathy is diagnosed or suspected.

In clinical studies, significant elevations of liver enzymes have been uncommon

- Increases in serum transaminase (greater than three times the upper limit of normal on two or more occasions) were seen in 1.3% of patients treated over an average of 18 months
- Elevations were generally reversible over time in patients discontinued from pravastatin; patients with biochemical findings were usually asymptomatic
- Active liver disease *or* unexplained transaminase elevations are contraindications to the use of pravastatin
- Liver function should be monitored before treatment and at recommended intervals–every 6 weeks for the first 3 months, every 8 weeks for the remainder of the first year, and periodically thereafter (e.g., at about 6-month intervals)

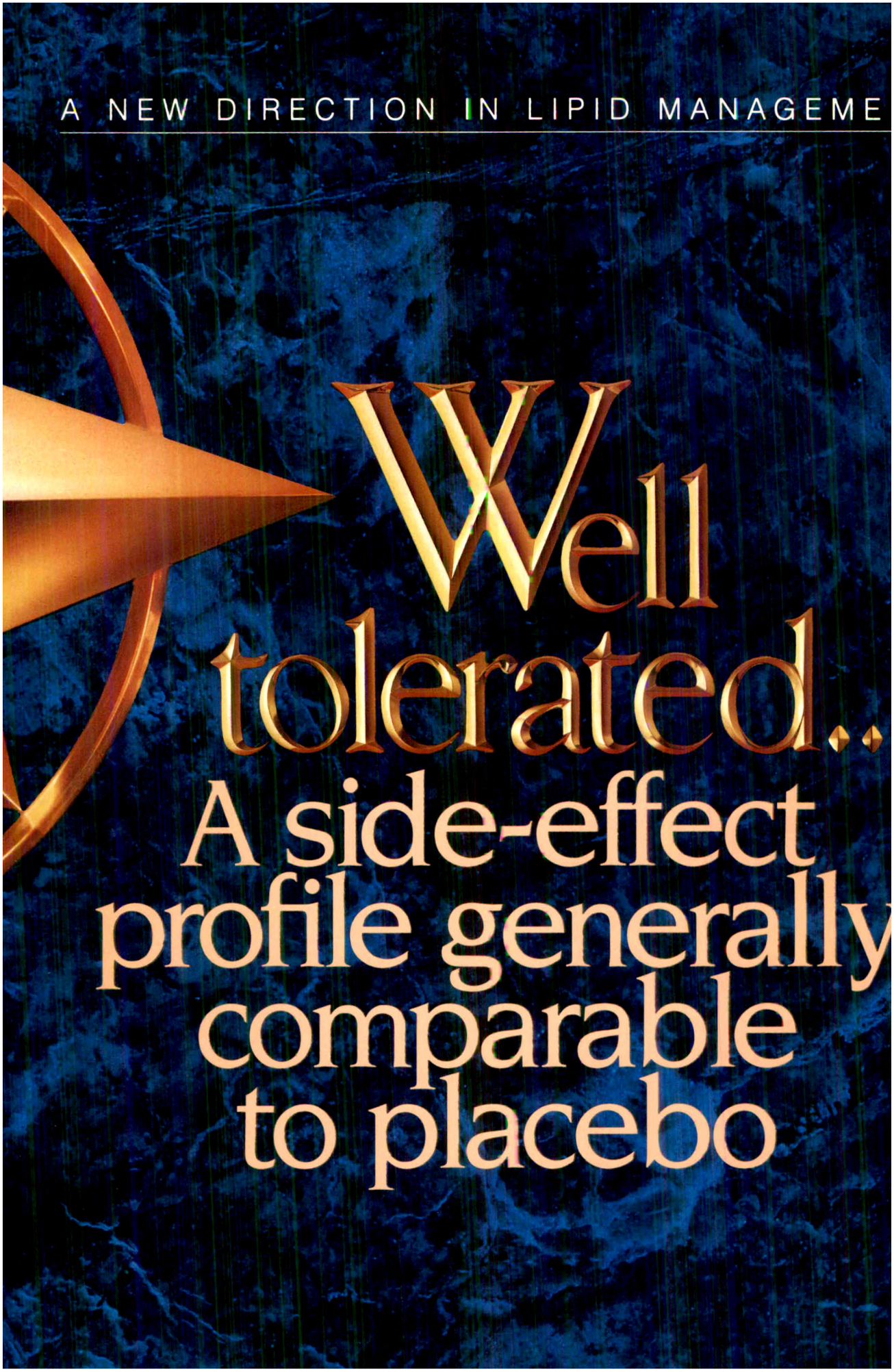
*A second patient developed myopathy when clofibrate was added to a previously well-tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.

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PRAVACHOL™

pravastatin sodium 20 mg tablets

A new direction in lipid management


A NEW DIRECTION IN LIPID MANAGEME
Well tolerated..
A side-effect profile generally comparable to placebo

Low incidence of side effects

Adverse clinical events attributed to study drug:	PRAVACHOL® (n = 900)	Placebo (n = 411)
Headache	1.7%*	0.2%
Cardiac chest pain	0.1	0.0
Rash	1.3	0.9
Nausea/vomiting	2.9	3.4
Diarrhea	2.0	1.9
Abdominal pain	2.0	3.9
Constipation	2.4	5.1
Flatulence	2.7	3.4
Heartburn	2.0	0.7
Fatigue	1.9	1.0
Chest pain	0.3	0.2
Localized pain	1.4	1.5
Myalgia	0.6	0.0
Dizziness	1.0	0.5
Urinary abnormality	0.7	1.2
Rhinitis	0.1	0.0
Cough	0.1	0.0

*Statistically different from placebo

Discontinuation rate from pravastatin (1.7%) was not statistically different from that of placebo (1.2%).

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PRAVACHOL™

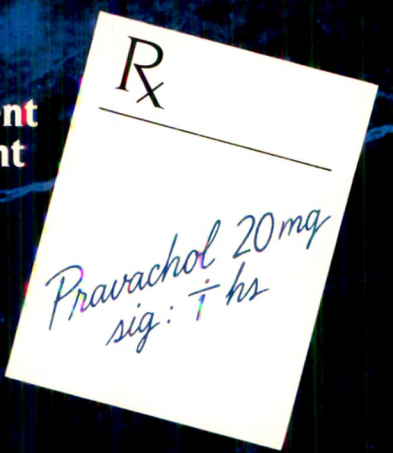
pravastatin sodium 20 mg tablets

A new direction in lipid management

BRISTOL-MYERS SQUIBB INTRODUCES

A NEW DIRECTION IN LIPID MANAGEMENT

New PRAVACHOL™ pravastatin sodium 20 mg tablets



Provides an exceptionally convenient regimen in cholesterol management —once-a-day bedtime dosing

PRAVACHOL® offers true once-a-day dosing at bedtime, with or without food.

Usual dose: 20 mg at bedtime, with or without food

Dosage range:
10-40 mg. Available in 10 and 20 mg tablets.

Excellent monotherapy for a wide range of patients

PRAVACHOL is suitable for patients with primary hypercholesterolemia (Types IIa and IIb) with a cholesterol-lowering diet when diet alone has not been adequate.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the final page of this advertisement.

References: 1. Data on file, Bristol-Myers Squibb. 2. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

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PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (< 0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The $AUC_{0\text{-}12hr}$ for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and t_{max} for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p < 0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥ 50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p < 0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p < 0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro,* with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae.* In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter²). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General.**)

ADVERSE REACTIONS

Pravastatin is generally well tolerated; adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is not associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. (J4-422A)

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Effects of Left Ventricular Dysfunction on the Circadian Variation of Ventricular Premature Complexes in Healed Myocardial Infarction

Anne M. Gillis, MD, Robert W. Peters, MD, L. Brent Mitchell, MD, Henry J. Duff, MD, Margot McDonald, BN, and D. George Wyse, MD

Circadian variation in the onset of cardiovascular events including sudden cardiac death, myocardial infarction and ventricular arrhythmias has been described. The effect of left ventricular (LV) dysfunction on the circadian variation of ventricular premature complex (VPC) frequency was evaluated in 132 patients with frequent VPCs and reduced LV function after myocardial infarction. Patients were prospectively divided in 2 groups based on LV ejection fraction (EF) (those with LVEF ≤0.30, and those with LVEF between 0.30 and 0.45). Median hourly VPC frequencies and heart rates were compared between the 2 groups. Subgroup analyses based on treatment with β-adrenoceptor blocking agents and on New York Heart Association functional class were also performed.

In patients with LVEF >0.30, a distinct circadian variation of VPCs, and the expected morning increase in VPC frequency were present. In contrast, a distinct circadian variation of VPCs was absent in patients with LVEF ≤0.30. A circadian variation of VPC frequency was also absent in patients with severe symptomatic congestive heart failure (New York Heart Association class III–IV). Treatment with β-adrenoceptor blocking agents was associated with a loss of the circadian variation of VPC frequency. The circadian variation of heart rate was also blunted in the group treated with β-adrenoceptor blocking agents. The proportion of subjects manifesting a positive correlation between heart rate and VPC frequency was lower in subjects with LVEF ≤0.30 (26%) than in those with LVEF >0.30 (46%) (p <0.05). Thus, circadian variation of VPC frequency is absent in patients with severe LV dysfunction.

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Circadian variation in the onset of cardiovascular events including sudden cardiac death, acute myocardial infarction, transient myocardial ischemia and thrombotic stroke has been previously described.[1–4] The greatest number of these cardiovascular events occur during the midmorning. In some data sets, some events (i.e., acute myocardial infarction) show a second peak in event frequency in the evening.[2,5] The frequency of ventricular premature complexes (VPCs) and ventricular tachycardia has also been reported to demonstrate a pattern consisting of a daytime peak and nighttime nadir.[6–8] It has been suggested that increased sympathetic tone associated with awakening or assuming the upright posture, or both, may be an important determinant of the variation in frequency of these cardiovascular events.[9,10] This latter rationale is supported by the observation that β-adrenoceptor blocking agents prevent or blunt the mid-morning peak of acute cardiac events.[11,12] Circadian variations of heart rate and blood pressure are also blunted in the settings of autonomic dysfunction[13] and chronic congestive heart failure.[14] The latter association may be mediated in part by increased circulating catecholamines associated with the heart failure syndrome.[15] Changes in VPC frequency are associated with those in heart rate,[16,17] but it is not known whether this association is dependent on changes in autonomic tone. The present study explores further the determinants of circadian variation of VPC frequency, especially left ventricular (LV) dysfunction.

METHODS

Study population: The study population comprised 132 consecutive patients (114 men and 18 women, mean age 63 ± 9 years) with a previous myocardial infarction, reduced left ventricular (LV) ejection fraction (EF) ≤0.45 and frequent VPCs (≥15/hour) documented by 24-hour ambulatory electrocardiography within 1 year of the index myocardial infarction. No patients were receiving class I or III antiarrhythmic drugs at the time of ambulatory electrocardiographic monitoring. Patients were prospectively divided in 2 groups based on LVEF: those with LVEF ≤0.30, and those with LVEF between 0.30 and 0.45.

Ambulatory electrocardiographic monitoring: A 2-channel recording with a minimum of 20 hours of analyzable data was obtained an average of 77 ± 84 days after admission for the index myocardial infarction. Recordings were analyzed by computer (Cardiodata Mark IV or Delmar Avionics 750A) with a manual overread by an experienced electrocardiographic technician. As

TABLE I Clinical Characteristics

	LVEF ≤0.30 (%)	LVEF >0.30 (%)
Sex (men/women)	42/11 (79/21)	72/7 (91/9)*
Age (yr)	63 ± 10	62 ± 9
Left ventricular ejection fraction	0.24 ± 0.05	0.37 ± 0.04†
Time after MI (days)	77 ± 76	77 ± 89
Drug therapy‡		
Digitalis	16 (34)	11 (14)*
β-blockers	9 (19)	19 (24)
Calcium antagonists	22 (47)	41 (52)
Clinical CHF§		
None	35 (68)	56 (72)
NYHA I–II	10 (20)	14 (18)
NYHA III–IV	6 (12)	8 (10)

*p <0.05; †p <0.001.
‡Drug therapy data not available for 6 patients with LVEF ≤0.30 and for 1 patient with LVEF >0.30.
§NYHA class not available in 3 patients.
CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; Time after MI = number of days after myocardial infarction before 24-hour ambulatory monitoring.

part of quality control procedures, electrocardiographic technicians were periodically required to read manually counted "gold standard" tapes. The accuracy for total VPC counts by technicians at the two centers was ±7%.

Hourly determinations of VPC frequency were normalized to 60 minutes based on the actual hourly analysis time. Hourly VPC frequency and heart rate were determined for each patient.

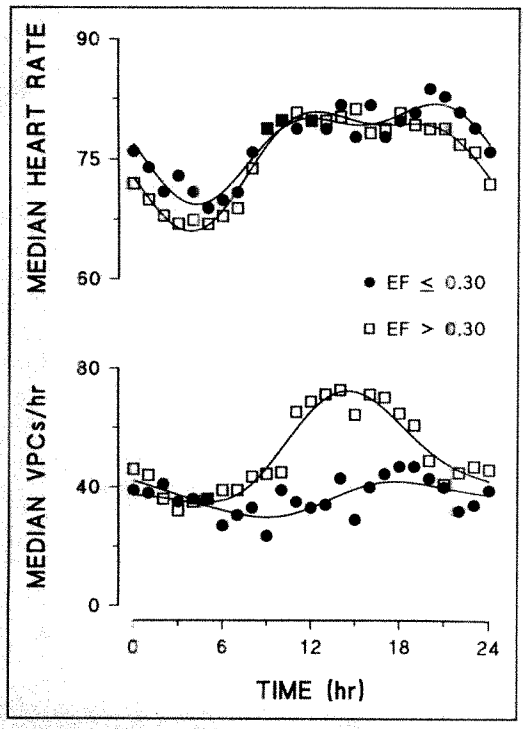


FIGURE 1. ***Top,*** **hourly median heart rate for patients according to left ventricular ejection fraction (EF): EF ≤0.30** ***(black dots)*** **and >0.30** ***(open squares).*** ***Bottom,*** **hourly median ventricular premature complex (VPC) frequency for patients according to left ventricular EF.** ***Curves*** **are fits of data to 2-harmonic cosinor function.**

Analysis of left ventricular function: LVEF was determined by radionuclide ventriculography with the use of the gated equilibrium technique in 111 patients, by contrast ventricular angiography in 6 and by echocardiography in 15. Patients were also examined by 1 investigator for determination of the presence or absence of clinical congestive heart failure and for assignment of New York Heart Association functional class.

Data analysis: To correct for skewed distributions and unequal variances, VPC frequency and heart rate data are presented as median values. Differences in VPC frequencies and heart rates were compared between the 2 LVEF groups. The influence of New York Heart Association functional class, and the use of β-adrenoceptor blocking agent therapy were assessed by subgroup analysis. Chronobiologic analysis of hourly VPC frequencies and heart rates used 2-harmonic regression analysis (equation 1)[18]:

$$\text{VPC or HR} = A - B\cos\frac{2\pi t}{24} - C\sin\frac{2\pi t}{24} - D\cos\frac{4\pi t}{24} - E\sin\frac{4\pi t}{24} \quad (1)$$

where t = time of day (hours), VPC = ventricular premature depolarization frequency/hour, and HR = heart rate.

The relation between heart rate and VPC frequency for individual patients was also evaluated. Linear regression analysis was applied to log (VPC + 1) versus heart rate for each patient who was then categorized as having a positive or negative log-linear correlation, or no correlation between arrhythmia frequency and heart rate.[16]

Statistical analysis: Median data are presented for heart rate and ventricular depolarization frequency. Other data are presented as mean ± standard deviation. Differences between groups were compared by the Wilcoxon rank sum test, unpaired *t* test or chi-square methods, as appropriate. The goodness of fit of the regression analysis of the cosinor function was assessed by the chi-square test. A 2-tailed p value <0.05 was considered significant.

RESULTS

Study population: Of the 132 patients with frequent VPCs and LV dysfunction after a recent myocardial infarction, 53 had LVEF ≤0.30. Their clinical characteristics and those of the remaining 79 patients with LVEF >0.30 are listed in Table I. Patients with lower LVEF were more likely to be women and receiving digoxin (p <0.05). Otherwise, the clinical characteristics of these 2 groups of patients were similar.

Circadian variation of ventricular premature complexes and left ventricular ejection fraction: A distinct diurnal variation of heart rate (described by a 2-harmonic cosinor function) was observed in each group (Figure 1). No significant differences in hourly heart rates were observed between these 2 groups. A distinct circadian variation of VPC frequency, and the expected morning increase in VPC frequency was observed in the

group with LVEF >0.30. In contrast, a significant variation of VPC frequency during the 24-hour monitoring period was not observed in the group with LVEF ≤0.30. The median hourly VPC frequency was not related to time of day in this group.

These patterns of diurnal variability become more distinct if patients receiving β-adrenoceptor blocking agents are excluded from the analysis. Hourly median heart rates and VPC frequencies for the 2 LVEF groups excluding patients receiving β-adrenoceptor blocking therapy are shown in Figure 2. Median hourly heart rates and their circadian pattern were similar between the 2 LVEF groups. However, the daytime VPC frequency was significantly greater in the group with LVEF >0.30 ($p < 0.05$), whereas no circadian variation of VPC frequency was evident in the other group (Figure 2, bottom).

Relations between heart rate and ventricular premature complex frequency: There are 3 possible relations between heart rate and VPC frequency: a positive or negative correlation, or no correlation. Individual examples of positive and negative correlations of the relation between heart rate and VPC frequency are shown in Figure 3. The relations between heart rate and VPC frequency for the 2 LVEF groups are shown in Table II. The proportion of patients manifesting a positive relation between VPC frequency and heart rate was significantly greater in the group with LVEF >0.30 ($p < 0.05$).

TABLE II Linear Regression Analysis of Log (ventricular premature complex + 1) and Heart Rate

	LVEF ≤0.30 (n = 53)	LVEF >0.30 (n = 79)
Positive correlation	14 (26%)	36 (46%)
Negative correlation	6 (11%)	9 (11%)
No correlation	33 (63%)	35 (43%)

Chi-square = 6.19; $p < 0.05$.
LVEF = left ventricular ejection fraction.

Circadian variation of ventricular premature complexes and congestive heart failure: To further evaluate the effects of LV dysfunction on circadian variation of VPC frequency, differences in hourly heart rates and VPC frequencies were compared between 115 patients with or without minimally symptomatic congestive heart failure (New York Heart Association functional classes I and II) and 14 with more significantly symptomatic congestive heart failure (classes III and IV). The median hourly heart rates for the New York Heart Association functional class I–II and III–IV patients are shown in Figure 4 (top). A circadian variation of heart rate is evident in both groups, although the magnitude of the variation is blunted in the subgroup with class III–IV heart failure. In this subgroup, heart rates tended to be greater during the nocturnal hours (2400 to 0300) than they were in patients with class I–II heart failure ($p < 0.09$). A circadian variation of VPC frequency was present in patients without heart failure or with class I–II heart failure (Figure 4, bot-

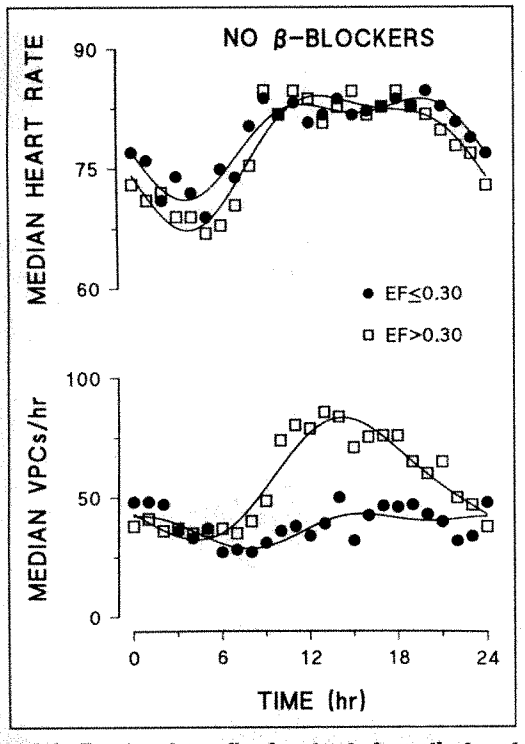


FIGURE 2. ***Top,*** **hourly median heart rate for patients not receiving β-adrenergic blocking agents based on left ventricular ejection fraction (EF): EF ≤0.30** ***(black dots)*** **and >0.30** ***(open squares). Bottom,*** **hourly median ventricular premature complex (VPC) frequency for patients not receiving β-adrenergic blocking agents based on left ventricular EF. Curves are fits of data to 2-harmonic cosinor function.**

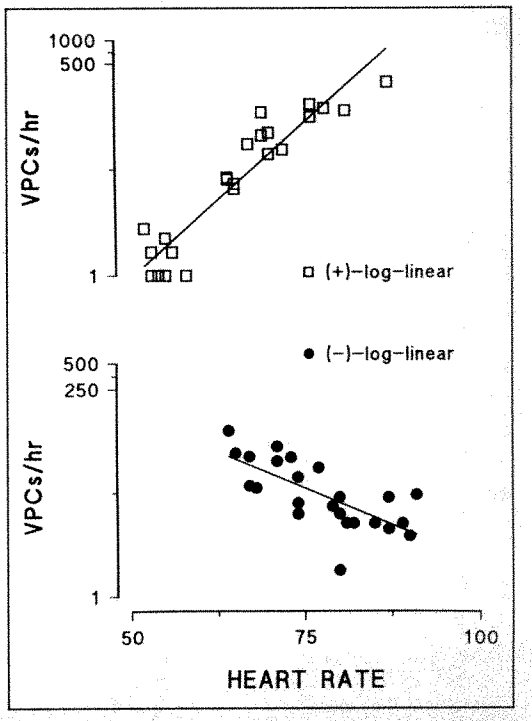


FIGURE 3. Examples of regression analysis of semilogarithmic plot of ventricular premature complex (VPC) frequency versus heart rate. Examples of positive ***(open squares)*** **and negative** ***(black dots)*** **log-linear relations are shown.**

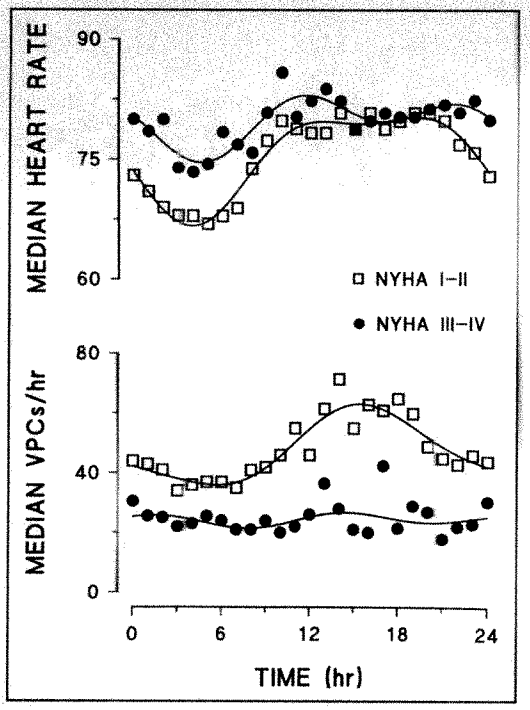


FIGURE 4. ***Top,*** **hourly median heart rate in 115 patients with no congestive heart failure or New York Heart Association (NYHA) functional class I–II symptoms** ***(open squares)*** **and in 14 with class III–IV heart failure** ***(black dots). Bottom,*** **hourly median ventricular premature complex (VPC) frequency according to symptoms of congestive heart failure.** ***Curves*** **are fits of data to 2-harmonic cosinor function.**

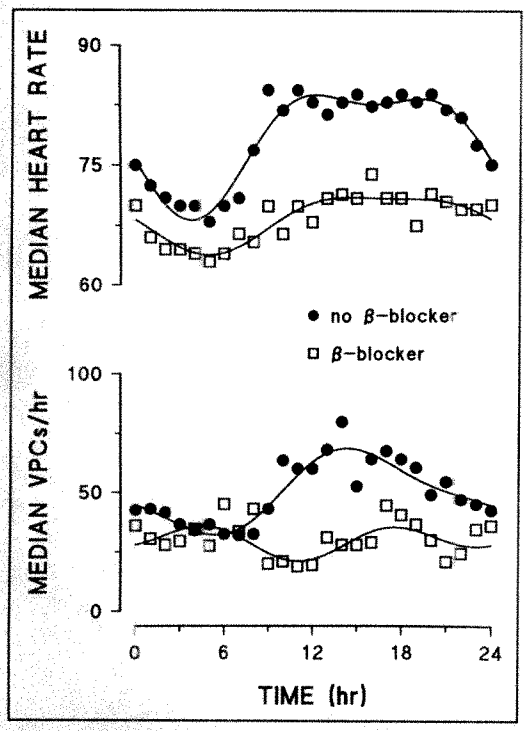


FIGURE 5. ***Top,*** **β-blocker therapy blunts circadian variation of heart rate.** ***Open squares:*** **patients receiving β-blockers (n = 28);** ***black dots:*** **patients not receiving β-blockers (n = 96).** ***Bottom,*** **circadian variation of ventricular premature complexes (VPCs) is absent in patients receiving β-blocker therapy.** ***Curves*** **represent fits of data to 2-harmonic cosinor function.**

tom). However, the expected circadian daytime increase in VPC frequency was absent in patients with class III–IV heart failure. Furthermore, the median hourly VPC frequencies were significantly lower during the day (1000 to 2400 hours) in patients with class III–IV heart failure than in those with class I–II ($p < 0.05$).

Circadian variation of ventricular premature complexes and β-adrenoceptor blocking agents: The median hourly heart rates for patients receiving β-adrenoceptor blocking agents and for those not receiving this therapy are shown in Figure 5 (top). A circadian rhythm of heart rate is evident in both groups, although its magnitude is blunted in the group receiving β-adrenoceptor blocking agents. Heart rate was significantly lower throughout the day in patients receiving β-adrenoceptor blocking agents than in those not receiving this therapy ($p < 0.05$). The median hourly VPC frequencies for patients receiving β-adrenoceptor blocking agents and for those not receiving these drugs are shown in Figure 5 (bottom). The expected circadian variation of VPC frequency was evident in the group not receiving β-adrenoceptor blocking agents. In contrast, no distinct circadian rhythm of VPC frequency was observed in the group receiving β-adrenoceptor blocking agents. The median hourly VPCs were significantly higher during the day (0900 to 2200 hours) in patients not receiving β-adrenoceptor blocking agents than in those receiving this therapy ($p < 0.05$).

DISCUSSION

The major new findings of the present study are as follows: (1) The expected circadian variation of VPC frequency is absent in patients with significant LV dysfunction after a recent myocardial infarction, and (2) the usual relation between changes in heart rate and changes in VPC frequency is altered in patients with significant LV dysfunction. We also confirmed that β-adrenoceptor blocking agents eliminate the expected circadian variation of VPC frequency.[19] These observations support the contention that autonomic tone is an important factor modulating circadian rhythms.

Circadian variation of ventricular premature complexes: There are conflicting reports concerning the circadian variation of VPC frequency. Some investigators reported a decrease in VPC frequency during sleep,[6,17] whereas others reported an increase in VPC frequency during sleep.[20,21] Furthermore, other investigators noted no difference in VPC frequency with sleep–wake or day–night intervals.[17,22] The present study identified at least 2 variables that may explain these conflicting reports: presence of significant LV dysfunction or use of β-adrenoceptor blocking agents, or both.

Circadian variation of ventricular premature complexes and ventricular function: The circadian variation of many cardiovascular functions and events (including heart rate, blood pressure and time of onset of myocardial infarction) have been reported to be altered in patients with congestive heart failure.[5,14] Although the mechanism(s) of this interaction may be multifactorial, neurohumoral factors should be considered. Plasma catecholamine levels manifest a circadian variation with

low levels at night, which increase on assumption of the upright posture.[9,10,23] Severe congestive heart failure is characterized by increased plasma catecholamines and β-adrenoreceptor down-regulation.[15,24] Persistent elevation of circulating catecholamines throughout the 24-hour period in patients with significant LV dysfunction could account for our observation of the absence of circadian variation in ventricular arrhythmia frequency in those with heart failure. Alternatively, reduced parasympathetic tone during the nocturnal period may explain the loss of circadian variation of VPC frequency in patients with severe LV dysfunction. In normal subjects, heart rate during sleep is predominantly controlled by parasympathetic nervous system activity, except during episodes of rapid eye movement sleep.[25] However, parasympathetic activity is significantly reduced in patients with severe ventricular dysfunction after myocardial infarction.[26,27] Loss of the nighttime predominance of parasympathetic activity may contribute to these altered circadian rhythms.

The patients with LVEF <0.30 and those with New York Heart Association functional class III–IV symptoms of heart failure tended to have fewer VPCs per hour than did the group with less severe LV dysfunction. Previous investigators reported that a greater proportion of patients with LVEF <0.30 have more frequent VPCs (>10/hour) than do those with a higher LVEF.[28] However, in the present study, only patients with VPCs of ≥15/hour were included. Thus, this selection criterion may explain the higher VPC frequency observed in patients with less severe LV dysfunction. Other factors such as the use of digitalis[29] or angiotensin-converting enzyme inhibitors[30] in the low LVEF group may have contributed to a reduction in VPC frequency.

Relations between heart rate and ventricular premature complex frequency: The relations between heart rate and VPC frequency were previously described by several investigators.[16,17] The most frequently observed relation was an increase in VPC frequency with increasing heart rate. We observed such a relation in 46% of patients with LVEF >0.30. However, only 26% of patients with LVEF ≤0.30 had this type of relation. This suggests that the relation between heart rate and VPC frequency is altered in the presence of ventricular dysfunction. The mechanism of this altered relation is not evident from our data. However, potential explanations include changes in autonomic nervous system activity[26,27] and nocturnal hypoxemia[21] in patients with heart failure.

Circadian variation of ventricular premature complex frequency and β-adrenoceptor blocking agents: The present study demonstrates that the circadian variation of heart rate is blunted and that the circadian variation of VPC frequency is eliminated in patients receiving β-adrenoceptor blocking therapy. This observation confirms previous reports that β-adrenoceptor blockers prevent the midmorning peak of ventricular arrhythmias[11,19] and suggests an important contribution of the sympathetic nervous system to the circadian variation of cardiovascular events.

Absence of physical activity could blunt circadian variations in patients with congestive heart failure. To minimize this potential in the present study, 24-hour electrocardiographic examinations were performed on ambulatory outpatients. Furthermore, we observed a prominent circadian variation of heart rate even in patients with severe LV dysfunction. Thus, the changes in circadian variation of VPCs are not explained by differences in activity levels.

More recent investigations of circadian rhythms include the presentation of wake-time–adjusted data. In the present study, the time of awakening was not recorded. However, because the time of awakening may vary considerably between individuals, future studies should include this type of analysis.

A circadian variation of sudden cardiac death with a morning peak was described by some investigators.[1,11] Likewise, a similar circadian variation of episodes of nonsustained ventricular tachycardia has been observed.[7,8] These patterns tend to disappear when day–night cycles are altered, and disruption of this pattern has been observed in patients in the hospital.[7] A circadian variation of sudden cardiac death is also absent in patients receiving β-adrenoceptor blocking therapy.[11] Our observations would predict that the circadian variation of sudden cardiac death would also be blunted in patients who have depressed LV function and altered autonomic regulation.

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Brief Summary

CARDENE®

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Capsules — For oral use

MECHANISM OF ACTION: CARDENE is a calcium entry blocker which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. The effects of CARDENE are more selective to vascular smooth muscle than cardiac muscle. In animal models, CARDENE produces relaxation of coronary vascular smooth muscle at drug levels which cause little or no negative inotropic effect.

CONTRAINDICATIONS: Patients with hypersensitivity to the drug. Because part of the effect of CARDENE is secondary to reduced afterload, the drug is also contraindicated in patients with advanced aortic stenosis.

WARNINGS: Increased Angina: About 7% of patients in short term placebo-controlled angina trials have developed increased frequency, duration or severity of angina on starting CARDENE or at the time of dosage increases, compared with 4% of patients on placebo. Comparisons with beta-blockers also show a greater frequency of increased angina, 4% vs 1%. The mechanism of this effect has not been established. (See ADVERSE REACTIONS.)

Use in Patients with Congestive Heart Failure: Although preliminary hemodynamic studies in patients with congestive heart failure have shown that CARDENE reduced afterload without impairing myocardial contractility, it has a negative inotropic effect *in vitro* and in some patients. Caution should be exercised when using the drug in congestive heart failure patients, particularly in combination with a beta-blocker.

Beta-Blocker Withdrawal: CARDENE is not a beta-blocker and gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8–10 days.

PRECAUTIONS: General: Blood Pressure: Careful monitoring of blood pressure during the initial administration and titration of CARDENE is suggested. CARDENE may occasionally produce symptomatic hypotension. Caution is advised to avoid systemic hypotension when administering the drug to patients who have sustained an acute cerebral infarction or hemorrhage. Because of prominent effects at the time of peak blood levels, initial titration should be performed with measurements of blood pressure at trough (just before the next dose) and at peak effect (1–2 hours after dosing).

Use in patients with impaired hepatic function: The drug should be used with caution in patients having impaired liver function or reduced hepatic blood flow. Patients with severe liver disease developed elevated blood levels (4-fold increase in AUC) and prolonged half-life (19 hours) of CARDENE.

Use in patients with impaired renal function: Mean plasma concentrations, AUC, and Cmax were approximately 2-fold higher in hypertensive mildly renally impaired patients treated with CARDENE than in healthy controls. Doses in these patients must be adjusted.

Drug Interactions: *Cimetidine:* Cimetidine increases CARDENE plasma levels. Patients receiving the two drugs concomitantly should be carefully monitored.

Digoxin: Some calcium blockers may increase the concentration of digitalis preparations in the blood. CARDENE usually does not alter the plasma levels of digoxin, however, serum digoxin levels should be evaluated after concomitant therapy with CARDENE is initiated.

Maalox: Co-administration of Maalox TC had no effect on CARDENE absorption.

Fentanyl Anesthesia: Severe hypotension has been reported during fentanyl anesthesia with concomitant use of a beta-blocker and a calcium channel blocker. Even though such interactions were not seen during clinical studies with CARDENE, an increased volume of circulating fluids might be required if such an interaction were to occur.

Cyclosporine: Concomitant administration of CARDENE and cyclosporine results in elevated plasma cyclosporine levels. Plasma concentrations of cyclosporine should therefore be closely monitored, and its dosage reduced accordingly, in patients treated with CARDENE.

When therapeutic concentrations of *furosemide, propranolol, dipyridamole, warfarin, quinidine,* or *naproxen* were added to human plasma (in vitro), the plasma protein binding of CARDENE was not altered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats treated for 2 years had a dose-dependent increase in thyroid hyperplasia and neoplasia. Mice treated for 18 months had no neoplasia or thyroid changes and dogs treated for 1 year had no thyroid pathology. There is no evidence of effects on thyroid function (plasma T4, TSW) in man. There was no evidence of mutagenic potential in a battery of tests, and no impairment of fertility in male or female rats.

Pregnancy: Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. CARDENE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is recommended that women who wish to breast-feed should not take this drug.

Pediatric Use: Safety and efficacy in patients under the age of 18 have not been established.

Use in the Elderly: Pharmacokinetic parameters did not differ between elderly hypertensive patients (≥65 years) and healthy controls after one week of CARDENE 20 mg TID. Plasma CARDENE concentrations in elderly hypertensive patients were similar to plasma concentrations in healthy young adult subjects when CARDENE was administered at doses of 10, 20 and 30 mg TID, suggesting that the pharmacokinetics of CARDENE are similar in young and elderly hypertensive patients. No significant differences in responses to CARDENE have been observed in elderly patients and the general adult population of patients who participated in clinical studies.

ADVERSE REACTIONS: In short-term (up to three months) studies 1,910 patients received CARDENE alone or in combination with other drugs. In these studies, adverse events were generally not serious but occasionally required dosage adjustment. Peak responses were not observed to be associated with adverse effects during clinical trials, but physicians should be aware that adverse effects associated with decreases in blood pressure (tachycardia, hypotension, etc.) could occur around the time of the peak effect.

Angina: The most common adverse events include pedal edema and dizziness in about 7% of patients; headache, asthenia, flushing and increased angina in about 6%; palpitations in about 3%; and nausea and dyspepsia in about 2%. Adverse events occurring in about 1% of patients include dry mouth, somnolence, rash, tachycardia, myalgia, other edema and paresthesia. Sustained tachycardia, syncope, constipation, dyspnea, abnormal ECG, malaise, nervousness and tremor occurred in less than 1% of patients.

In addition, adverse events were observed which are not readily distinguishable from the natural history of the atherosclerotic vascular disease in these patients. Adverse events in this category each occurred in <0.4% of patients receiving CARDENE and included myocardial infarction, atrial fibrillation, exertional hypotension, pericarditis, heart block, cerebral ischemia and ventricular tachycardia. It is possible that some of these events were drug-related.

Hypertension: The most common adverse events include flushing in about 10% of patients; headache and pedal edema in about 8%; asthenia, palpitations and dizziness in about 4%; tachycardia in about 3%; nausea in about 2%; and somnolence in 1%. Dyspepsia, insomnia, malaise, other edema, abnormal dreams, dry mouth, nocturia, rash and vomiting occurred in less than 1% of patients.

Additionally, the following rare events have been reported: infection, allergic reaction, hypotension, postural hypotension, atypical chest pain, peripheral vascular disorder, ventricular extrasystoles, ventricular tachycardia, sore throat, abnormal liver chemistries, arthralgia, hot flashes, vertigo, hyperkinesia, impotence, depression, confusion, anxiety, rhinitis, sinusitis, tinnitus, abnormal vision, blurred vision, increased urinary frequency.

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Comparison of the Plasma Levels of Apolipoproteins B and A-1, and Other Risk Factors in Men and Women with Premature Coronary Artery Disease

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The predictors of premature coronary atherosclerosis were examined in 203 patients (99 men aged ≤50 years, and 104 women aged ≤60 years) undergoing elective diagnostic coronary arteriography. Age, cigarette smoking, hypertension, obesity, diabetes, positive family history of premature coronary artery disease (CAD), and plasma levels of total cholesterol, triglyceride, lipoproteins (i.e., very low, intermediate-, low-, and high-density [HDL] lipoproteins and their subfractions [HDL_2 and HDL_3], and lipoprotein [a]) and apolipoproteins (apoA-1, apoA-2 and apoB, respectively) were examined using univariate analyses and multivariate logistic regression. In men, age ($p < 0.05$), smoking ($p < 0.05$), and plasma triglyceride ($p < 0.02$) and apoA-1 ($p < 0.05$) levels were independently associated with CAD. In women, smoking ($p < 0.001$) and plasma apoB levels ($p < 0.04$) were the strongest variables independently associated with CAD. It is concluded that the "nontraditional" risk factors (plasma apoA-1 and apoB levels) are better predictors of premature CAD than are plasma lipoproteins and that smoking is the strongest of the traditional nonlipid risk factors.

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The plasma levels of total, low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterols, and triglyceride are usually higher, whereas those of high-density lipoprotein (HDL) cholesterol and its 2 major subfractions (HDL_2 and HDL_3 cholesterols) are usually lower in patients with than in those without coronary atherosclerosis (defined by coronary arteriography).[1–10] In some but not all reports, nonlipid risk factors such as increased blood pressure, cigarette smoking, diabetes and excess body weight were also considered. Only approximately half of coronary artery disease (CAD) is explained by these lipid- and nonlipid-related risk factors.[11] Thus, more recent studies also measured plasma levels of apolipoproteins B and A-1 (apoB and apoA-1; the major proteins of LDL and HDL, respectively), and lipoprotein (a) [Lp(a)], a plasma lipoprotein consisting of an LDL molecule covalently bound to apolipoprotein (a), a protein homologous to plasminogen.[2–10] However, less comparative information is available in subjects (particularly women) with premature coronary atherosclerosis.

METHODS

Study population: The study population comprised 99 white men (aged ≤50 years) and 104 white women (aged ≤60 years) who underwent elective, diagnostic coronary arteriography at the Johns Hopkins Hospital between April 1985 and April 1988. Sixty years was chosen as the cut point in women, because they generally present with premature CAD 10 years later than men, and very few women aged <50 years undergo coronary arteriography.[1,12,13] The number of nonwhite subjects was too small to constitute a subgroup, and thus only white subjects were studied. Patients were excluded for the following reasons: age, distance (lived >100 miles from the Johns Hopkins Hospital), undergoing unscheduled or emergent cardiac catheterization or coronary angioplasty, receiving lipid-lowering medication or had a myocardial infarction within the previous 12 weeks. Ninety-three percent of the men, and 91% of the women who were eligible and were contacted agreed to participate in the study. Informed consent was obtained from each participant. The study was approved by the Johns Hopkins Joint Committee on Clinical Investigation.

Patients were recruited for the study as follows. Each week a complete list of age- and sex-eligible patients scheduled for elective arteriography was obtained

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from the catheterization laboratory. Potentially eligible patients were approached systematically, starting with the beginning of the list and proceeding down. No more than 4 subjects were studied each week, because of the time limitation posed by the large number of laboratory analyses needed for the study. Eighty-eight of the men (88.8%), and 89 of the women (85.5%) underwent angiography for evaluation of ischemic heart disease (typical angina or a positive exercise tolerance test, or both); 10% of the men, and 13.5% of the women had arteriography for valvular heart disease.

Definitions of coronary artery disease: To insure misclassification of <3%,[12,13] coronary arteriograms were reviewed by a panel of 3 cardiologists who had no prior knowledge of the clinical history or laboratory data of patients. The presence of stenosis in the 15 coronary artery segments designated by the American Heart Association was determined.[14] CAD was considered to be present if ≥1 lesion narrowed the lumen of any of the 15 coronary arterial segments by ≥50%. Patients with such lesions were considered to be cases, whereas those without narrowings ≥50% were considered to be control subjects. The study group was further divided into patients with 0, 1, 2 or 3 diseased coronary arteries according to the number of major coronary arteries (right, left anterior descending or left circumflex) that had ≥50% diameter narrowings). Quantitative digital methods were not used to assess the extent of coronary atherosclerosis. Visual interpretation of an arteriogram generally provides an underestimation of coronary atherosclerosis.[1] Analyses related to risk factors, number of diseased vessels, and a continuous score of CAD will be the subject of a separate report.

Plasma lipid, lipoprotein and apolipoprotein determinations: BLOOD COLLECTION: After a 12-hour fast, blood (60 ml) was drawn into evacuated tubes containing disodium ethylenediaminetetraacetic acid (1.5 mg/ml of blood), cooled to 4°C and transported to the Johns Hopkins Lipoprotein Analytical Laboratory. Cells were removed by centrifugation (1,500 × g, 30 minutes, 4°C) within 3 hours of collection, and plasma was stored at 4°C before analysis or at −70°C (for Lp(a) and apoA-2 measurements). Leukocytes were harvested for isolation of DNA.

TOTAL AND HIGH-DENSITY LIPOPROTEIN CHOLESTEROLS: Cholesterol in plasma and the lipoprotein fractions was determined enzymatically as described previously.[15] Total HDL cholesterol was determined after precipitation of the apoB-containing lipoproteins with heparin and manganese chloride. When patients were sampled, manganese chloride was used at a final concentration of 0.046 M; this was changed to 0.092 M for the analysis of HDL cholesterol in the relatives of the patients, because the lower concentration does not completely precipitate apoB-containing lipoproteins.[16] To allow a correction for the incomplete precipitation, a separate substudy was performed in which 188 relatives of patients had HDL cholesterol measured using both concentrations of manganese chloride. The lower concentration gave a positive mean bias of 3.1 ± 0.3 mg/dl. The bias was independent of HDL cholesterol concentration ($r = 0.018$). The HDL cholesterol concentrations in patients were therefore corrected by subtracting 3 mg/dl from the measured values.

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL SUBFRACTIONS: Four milliliters of the heparin–manganese chloride supernate was adjusted to a density of 1.125[17] and centrifuged at 105,000 × g for 40 hours, the bottom fraction containing HDL_3 was recovered by tube slicing, and its cholesterol concentration was determined. HDL_2 cholesterol was calculated as the difference between total HDL and HDL_3 cholesterol.

VERY LOW, INTERMEDIATE- AND LOW-DENSITY LIPOPROTEIN CHOLESTEROLS, AND TRIGLYCERIDE: Plasma (5 ml), at its own density (1.006 g/ml), and plasma (10 ml) after adjustment to d 1.019 g/ml with liquid potassium bromide (17), were centrifuged at 105,000 × g for 18 hours. The infranate fractions were collected by tube slicing, and their cholesterol contents were determined. VLDL cholesterol was calculated by subtracting the cholesterol in the 1.006 g/ml infranate from the plasma total cholesterol. IDL cholesterol was calculated as the difference between the cholesterol in the 1.006 and 1.019 g/ml infranates. LDL cholesterol was calculated as the difference between the cholesterol in 1.019 g/ml infranate and total HDL cholesterol. Plasma triglyceride was measured enzymatically.[15]

APOLIPOPROTEIN MEASUREMENTS: ApoA-1 and ApoB levels were measured by radial immunodiffusion, as described previously.[15] ApoA-2 was measured in frozen plasma by radial immunodiffusion in 10% agarose, using an antibody to apoA-2, and serum pools with known apoA-2 levels obtained as gifts from John Albers, PhD. Plasma was diluted 10-fold and applied to the wells. Ring diameters were measured after 72 hours. The assay for apoA-2 had a coefficient of variation of 6.1%. Lp(a) was measured on frozen plasma using a monoclonal antibody-based sandwich enzyme-linked immunosorbent assay[18] available commercially (MACRA Lp(a) Terumo, Elkton, Maryland). The coefficient of variation for Lp(a) was 6.9%, and the method does not detect plasminogen.[18]

OTHER RISK FACTORS AND CLINICAL DATA: Interviews were conducted and clinical data collected using a common protocol and standardized forms.[12,19,20] Medications used during the preceding 2 weeks were recorded. Hypertension was defined as a self-reported history of high blood pressure, or treatment with antihypertensive agents. Cigarette smoking was categorized as ever versus never smoked. Current smoking was defined as smoking cigarettes within the past month. Weight and height (without shoes) were measured using a standard scale and recorded to the nearest tenth of a kilogram or centimeter. Family history of premature CAD (defined as myocardial infarction [fatal or nonfatal] or angina pectoris before the age of 60 years in either parent) was obtained by questionnaire. Blood (3 ml) was collected in fluorinated tubes, and glucose determined at the Johns Hopkins Clinical Chemistry Laboratory using a glucose oxidase method. Diabetes was defined as a fasting blood sugar >140 mg%[21] or a diagnosis of diabetes needing diet or drug therapy.

TABLE I Characteristics of Subjects Undergoing Coronary Arteriography for Premature Atherosclerosis

	Men (n = 99)*	Women (n = 104)*
Age (yr)	44	52
Range	24–50	36–60
Coronary arteries		
Narrowed ≥ 50% in diameter (any)	61%	49%
1†	14%	13%
2	15%	15%
3	31%	23%
Previous myocardial infarction	24%	26%
Positive Rose questionaire	41%	40%
Stroke	2%	5%
H/O hypertension	45%	54%
Diabetes mellitus	8%	17%
Ever smoked cigarettes	76%	59%
Current cigarette smokers	20%	24%

*Questionaire data available from 97 men and 103 women.
†In 8 angiograms, coronary atherosclerosis was present, but not all vessels were completely visualized.
H/O = history of.

TABLE II Medication Use by Subjects

Medications Taken in Previous 2 Weeks	Men (n = 97)	Women (n = 103)	Total (n = 200)
β blockers	44	44	88 (44.0%)
Calcium antagonists	37	50	87 (43.5%)
Diuretics	17	34	51 (25.6%)
Long-acting nitroglycerins	15	33	48 (24.0%)
Digitalis preparations	5	13	18 (9.0%)
Antiarrhythmics	4	8	12 (6.0%)
Thyroid medications	2	8	10 (5.0%)
Other hormones	0	10	10 (5.0%)
Anticoagulants	0	9	9 (4.5%)
Corticosteroids	2	3	5 (2.5%)
Oral contraceptives	0	1	1 (0.5%)
Cholesterol-lowering agents	0	0	0 (0.0%)

Statistical analyses: Univariate distributions of all variables were examined, and all outliers confirmed. The association of lipid and other risk factors with CAD was studied using logistic regression for men and women separately, and for the entire study population. Because patients with CAD were older than those without CAD, measures of association were adjusted for age. The age-adjusted p value and the correlation coefficient for each risk factor were calculated from a logistic regression model with CAD as the dependent variable, and age and the risk factor of interest as the independent variables. All continuous variables were divided into quartiles and examined as categorical variables. The results of the continuous and categorical analyses were similar. Therefore, only the continuous models are presented.

Multivariate logistic regression models were constructed by considering all the variables that were associated with CAD after adjustment for age only. Odds ratios for continuous variables were calculated for a 1 SD difference in the variable. This allows for comparison of the strength of association of CAD with different variables.

RESULTS

Characteristics of study population: The characteristics of the study population are summarized in Table I. A higher proportion of men than women had premature and more severe (3-vessel) CAD, but these differences did not reach statistical significance. In subjects without CAD, the distribution of the most severely affected segment <50% was as follows: no lesion (70.1%), 1 to 20% lesion (17.2%), 21 to 40% lesion (12.6%) and 41 to 49% lesion (none). History of hypertension and diabetes was more prevalent in women than in men.

Medication use: The most frequently taken medications in the previous 2 weeks (in order of use) were: β blockers, calcium antagonists, diuretics and long-acting nitroglycerines (Table II). The mean differences between subjects with and without CAD in the plasma levels of total and HDL cholesterols, triglyceride, apoB and apoA-1 were similar ($p > 0.10$) between subjects receiving and not receiving any 1 of these medications.[22]

Association of lipid-related variables with premature coronary atherosclerosis: For men, the plasma levels of total cholesterol, triglyceride, apoB in plasma and d >1.006 g/ml infranate, and apoA-1 were significant univariate discriminators of CAD (Table III). However, after adjusting for age, only the triglyceride and apoA-1 levels remained significant predictors of CAD in men (Table III). The results in women differed from those in men. First, before adjustment for age, the plasma levels of total, VLDL, and total HDL and HDL_3 cholesterols, triglyceride, and apoB in whole plasma and in d >1.006 and >1.019 g/ml infranates, and apoA-2 were all significantly associated with CAD (Table III). Adjustment for age removed only total HDL cholesterol and plasma apoA-2 as significant indicators of premature CAD in women. The ratio of plasma apoB to apoA-1 was significantly associated with premature CAD in both men and women (Table III). Lp(a) levels were higher in those with than in those without CAD, but did not reach statistical significance.

Because the levels of apoB were clearly stronger indicators of CAD in women than in men, whereas the level of apoA-1 was stronger in men, the distributions of plasma levels of these apolipoproteins were examined. For men, the plasma apoB levels were shifted toward higher values in those with CAD (Figure 1), whereas in women, the distribution of plasma apoB levels in those with CAD appeared bimodal (Figure 1). The distribution of plasma apoA-1 levels was shifted toward lower values in men with CAD; in contrast, the distributions of apoA-1 levels in the women with and without premature CAD were much broader and relatively similar (Figure 1).

Multivariate analysis of lipid-related discriminators and premature coronary artery disease in men and women: Logistic regression models showed that the plasma apoB level was more closely associated with CAD than were total and LDL cholesterols, or apoB in the 1.006 and 1.019 g/ml infranates among men, women and the total study population. When each of the latter variables was modeled simultaneously with plasma apoB (and age), the association of plasma apoB

TABLE III Association of Plasma Levels (mg/dl) of Lipids, Lipoprotein Cholesterols and Apolipoproteins with Premature Coronary Atherosclerosis in Men and Women

	Men				Women			
	With CAD (n = 60)	Without CAD (n = 39)	Unadjusted p Value*	Age-Adjusted p Value†	With CAD (n = 51)	Without CAD (n = 53)	Unadjusted p Value*	Age-Adjusted p Value†
Age (yrs)	45.8	41.5	0.0001‡	—	53.9	51.8	0.06	—
Total cholesterol	240	221	0.04	0.30	255	220	0.0007	0.002
VLDL cholesterol	53	45	0.20	0.69	55	37	0.005	0.007
IDL cholesterol	16	15	0.69	0.74	18	13	0.18	0.31
LDL cholesterol	127	119	0.35	0.68	135	119	0.09	0.07
HDL cholesterol	46	48	0.60	0.57	51	58	0.03	0.06
HDL_2 cholesterol	17	16	0.68	0.84	21	24	0.27	0.35
HDL_3 cholesterol	31	33	0.28	0.23	31	36	0.03	0.03
Triglyceride§	208	143	0.0004	0.006	202	128	0.009	0.014
Plasma apoB	153	135	0.01	0.13	159	126	0.0001	0.0003
ApoB > 1.006 g/ml	135	119	0.02	0.13	139	110	0.0004	0.0016
ApoB > 1.019 g/ml	127	119	0.31	0.66	135	110	0.003	0.007
Plasma apoA-1	131	147	0.02	0.02	147	163	0.07	0.09
Plasma apoA-2	28	28	0.69	0.93	27	28	0.04	0.07
Lp(a)	19	15	0.43	0.29	19	12	0.07	0.09
Plasma apoB/apoA-1	1.23	0.97	0.002	0.02	1.17	0.82	0.0001	0.0001

*Unadjusted p value from Student's *t* test.
†Adjusted for age only in logistic regression model.
‡p values ≤0.05 level are underlined.
§Triglyceride values were log transformed for 2 reasons. First, they were markedly skewed toward high values ($p < 0.01$). Second, log triglyceride was more strongly associated with CAD, indicating that log transformation allowed for better description of its association with CAD. Values reported are antilog of result in log scale.
The following measurements were not performed in indicated number of samples: VLDL (n = 1), IDL (n = 2), LDL (n = 3), HDL (n = 1), HDL_2 (n = 17), HDL_3 (n = 16), plasma apoB (n = 3), apoB in d > 1.006 g/ml (n = 1), apoB in d > 1.019 g/ml (n = 3), apoA-1 (n = 1), apoA-2 (n = 36), Lp(a) (n = 31) and apoB/apoA-1 (n = 4).
Apo = apolipoprotein; CAD = coronary artery disease; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; Lp (a) = lipoprotein (a); VLDL = very low density lipoprotein.

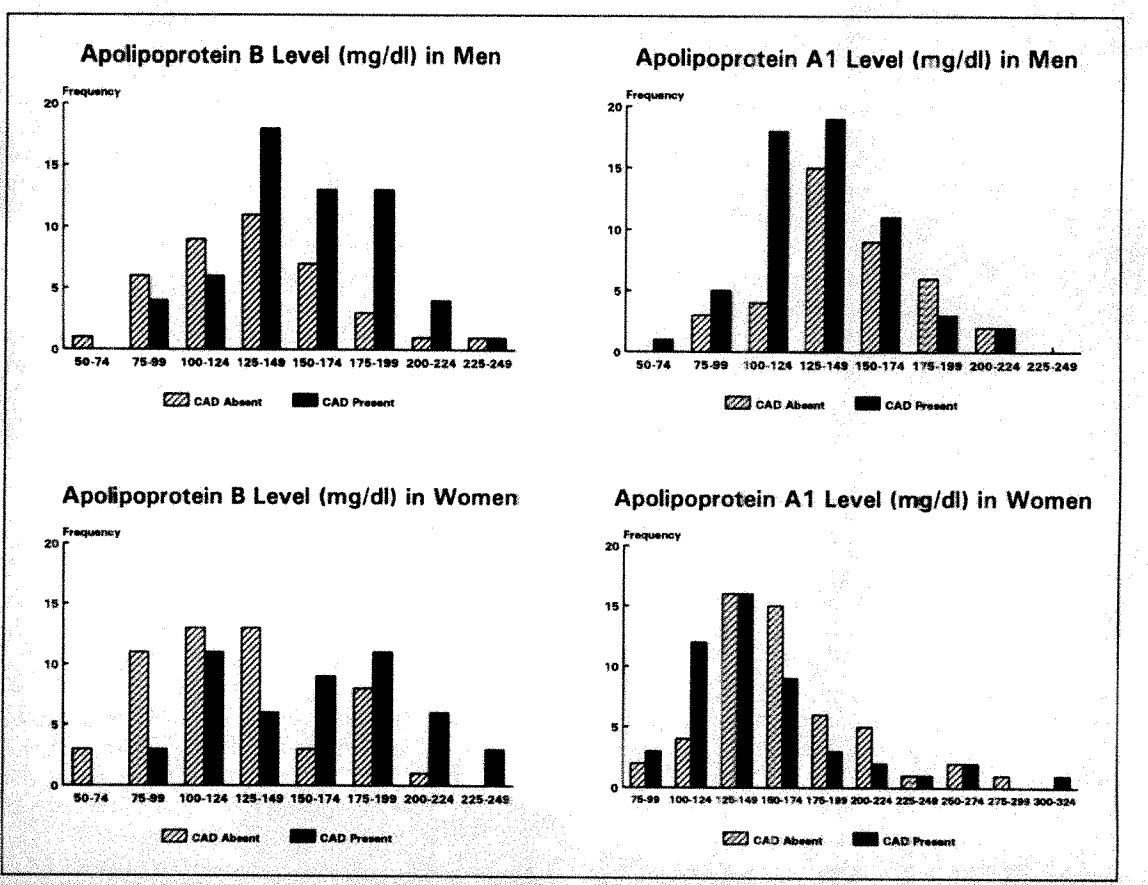


FIGURE 1. The distributon of plasma levels of apolipoproteins B (*left*) and A-1 (*right*) in men (*top*) and women (*bottom*) with (*black bars*) and without (*crossed-hatched bars*) coronary artery disease (CAD).

TABLE IV Multivariate Comparison of Plasma Levels of Lipids, Lipoprotein, Cholesterol and Apolipoproteins as Predictors of Premature Coronary Atherosclerosis in Men and Women

	Men (n = 98)		Women (n = 101)	
Variable	r Value	p Value*	r Value	p Value*
Age	0.236	0.002	0.000	0.24
Triglyceride†	0.190	0.009	0.064	0.11
Plasma apoB	0.000	0.258	0.195	0.007
Plasma apoA-1	−0.150	0.026	0.000	0.29

*p values < 0.05 are underlined.
†Triglyceride values were log transformed.
Correlation coefficient (r) is from multiple logistic regression.
apo = apolipoprotein.

TABLE V Association of Nonlipid Risk Factors with Premature Coronary Atherosclerosis in Men and Women

	Men (n = 97)			Women (n = 103)		
	With CAD	Without CAD	p Value*	With CAD	Without CAD	p Value*
H/O hypertension	51%	37%	0.39	62%	47%	0.15
Diabetes	15%	3%	0.20	27%	8%	0.03
Ever smoked	88%	58%	0.005	82%	38%	0.0001
Fasting blood sugar (mg/dl)	101	90	0.36	109	99	0.39
Body mass index (kg/m^2)	28	28	0.74	26	26	0.83
Family history of CAD before age 60 years†						
Father	29%	28%	0.74	22%	24%	0.83
Mother	5%	13%	0.17	15%	18%	0.83
Either parent	28%	34%	0.28	33%	37%	0.82
Both parents	2%	6%	0.62	4%	2%	0.81

*Age-adjusted p value from a logistic regression; values < 0.05 are underlined.
†Family history of CAD, defined as myocardial infarction (fatal or nonfatal) or angina pectoris.
The following measures were not performed in the indicated number: fasting blood sugar (n = 5) and family history (n = 25).
CAD = coronary artery disease; H/O = history of.

with CAD was stronger, and the association between the other risk factor and CAD was weak and not statistically significant. The only exception to this statement was that among men, plasma apoB and apoB in the 1.006 g/ml infranate were equally associated with CAD. Similarly, the log of plasma triglyceride was more closely associated with CAD than was plasma VLDL, log of plasma VLDL or plasma triglyceride levels before log transformation. ApoA-1 was more closely associated with CAD in men, women and the total sample than were HDL and HDL_2 cholesterols. However, HDL_3 cholesterol was more closely associated with CAD than was apoA-1 among women ($p = 0.08$ and 0.53, respectively, when HDL_3 and ApoA-1 were modeled simultaneously with age). The significance of this finding is uncertain, particularly because neither apoA-1 nor HDL_3 were associated with CAD in women after adjustment for plasma apoB level. For men, age, log triglyceride and apoA-1 levels were independently associated with CAD, whereas the additional contribution of plasma apoB level was not statistically significant (Table IV). In women, plasma apoB level was the best indicator for CAD. Log triglyceride was mildly associated and apoA-1 levels were only weakly associated with CAD after adjustment for apoB level (Table IV).

Menopausal status and plasma apolipoprotein B levels in women: Sixty-one women (59%) in the study were postmenopausal, whereas eighteen (17%) were premenopausal. Menopausal status could not be determined for 24 women (23%) who had hysterectomies. Plasma apoB level was higher in the 36 postmenopausal women with CAD than in the 25 without CAD (156 vs 132 mg/dl; $p = 0.03$). Among premenopausal women, this difference was even more striking (mean plasma apoB level 184 mg/dl in those with ($n = 3$) vs 114 mg/dl in those without ($n = 16$) CAD; $p = 0.01$). Thus, plasma apoB level was associated with CAD in both pre- and postmenopausal women, and the association may be stronger for premenopausal ones.

Association of nonlipid risk factors with premature coronary artery disease: We next determined whether nonlipid risk factors such as hypertension, diabetes, smoking, family history of premature myocardial infarction, and so forth were significantly associated with premature CAD (Table V). Using univariate analysis, history of ever smoking was strongly and significantly associated with premature CAD in both men and wom-

TABLE VI Multiple Logistic Regression Models of Lipid- and Nonlipid-Related Risk Factors as Predictors of Premature Coronary Atherosclerosis in Men and Women

	All (n = 196)				Men (n = 96)*				Women (n = 100)*			
Variable	OR	95%	CI	p Value†	OR	95%	CI	p Value†	OR	95%	CI	p Value†
Age (10 yrs)	2.7	1.3	5.5	0.007	8.4	1.9	36.9	0.01	1.8	0.7	4.2	0.2
Smoking (ever)	5.0	2.3	10.7	0.001	3.3	1.0	11.1	0.05	6.0	2.2	16.6	0.001
Triglyceride (0.3 logs)‡	1.7	1.1	2.7	0.011	2.4	1.1	5.2	0.02	1.5	0.9	2.6	0.13
ApoB (40 mg/dl)	1.6	1.1	2.4	0.016	1.4	0.8	2.6	0.27	1.7	1.0	2.9	0.04
ApoA-1 (40 mg/dl)	0.8	0.5	1.1	0.16	0.5	0.3	1.0	0.05	0.9	0.6	1.4	0.60
Sex (men)	2.3	0.9	5.8	0.08								

*Three men and 4 women were not included due to missing data.
†p values < 0.05 are underlined.
‡Triglyceride levels were log transformed.
Apo = apolipoprotein; CI = confidence interval; OR = odds ratio.

en. The other variables did not differ significantly between men with and without CAD ($p > 0.05$). In women (but not in men) history of diabetes reached statistical significance (Table V).

Consideration of the strongest lipid- and nonlipid-related variables simultaneously: Using multiple logistic regression models, plasma levels of apoB and apoA-1 were better predictors of CAD than was LDL or HDL cholesterol (and subfractions) for the entire study population (Table VI). Total cholesterol level was not a predictor of CAD after adjustment for the plasma apoB levels, but triglyceride level remained a significant indicator of premature CAD. Smoking and age were strong, nonlipid predictors (Table VI). For men, triglyceride level followed by apoA-1 were the best lipid-related predictors, whereas for women, plasma apoB was the best independent lipid predictor (Table VI). Ever smoking remained a strong, independent predictor of premature CAD in both men and women.

DISCUSSION

There are few, if any, previous studies of a comparable number of women with premature CAD. The plasma apoB level was the strongest indicator of premature CAD in these women. Data from prospective studies indicated that total cholesterol level was clearly an important predictor of CAD among women as well as men, whereas the association of LDL cholesterol level with CAD in women was less clear.[23] Our findings were consistent with these studies. An increased number of small, dense LDL particles (hyperapoB)[24] is often accompanied by increased levels of VLDL cholesterol and triglyceride. Plasma apoB seems even higher in premenopausal women with CAD, indicating the influence of an endogenous (perhaps genetic) factor on apoB levels that was not obviated (or prevented) by the presence of female hormones. Campos et al[25] found that postmenopausal women had significantly smaller LDL-particle size than did premenopausal ones, but such differences were not associated with significant changes in apoB levels. Interestingly, in a study of black men and women catheterized for chest pain and an abnormal stress test, Ford et al[26] found that plasma apoB levels were more strongly associated with CAD in women than men. In an older (mean age 60 years) group of 37 women, Sedlis et al[3] found that only triglyceride and apoB levels correlated with severity of CAD. Reardon et al[8] reported that CAD in women was related to triglyceride, cholesterol and apoB concentrations in IDL.

The bimodal distribution of plasma apoB levels in women with premature CAD suggests strongly the influence of a major gene. Further family studies in the relatives of these index cases should elucidate this hypothesis and determine more precisely the etiologic heterogeneity of genetic factors (such as the contribution of the genes for hyperapo and familial combined hyperlipidemia).[27]

The dyslipidemic pattern in men with premature CAD generally differed from that in women. First, age adjustment removed much of the association of plasma apoB with CAD in men; a low level of apoA-1, and a high level of triglyceride were the best indicators of CAD. The significantly lower level of apoA-1 in men with premature CAD was clearly not accompanied by a lower level of HDL cholesterol (or its subfractions). In a previous angiographic study,[13] we also found that plasma total HDL cholesterol did not significantly predict the presence of 1-, 2- or 3-vessel CAD in men aged 30 to 49 years, but did so in those aged 50 to 70.[13] More recently, Hearn et al[2] similarly found that older men (mean age 57 years) with CAD had lower HDL cholesterol levels. In agreement with our previous report of another cohort, plasma levels of total HDL cholesterol in women with premature CAD was significantly lower than in those without CAD.[21] In the present study, this observation was expanded to include levels of HDL_3 cholesterol and apoA-1, which were also lower in women with premature CAD.

Hypertension, diabetes and cigarette smoking were more prevalent in those with than without premature CAD in both men and women (Table V). However, cigarette smoking emerged as the strongest nonlipid risk factor. The magnitude of the association between smoking and CAD was comparable to the strongest lipid-related risk factors. After considering the influence of triglyceride, apoB and apoA-1 levels, smoking remained independently associated with premature CAD. The inability of some studies[1,2,5] to find such a significant contribution of smoking to CAD may be related to the size or nature of the control groups, or to not using ever smoking instead of current smoking.

We are unable to explain why there was so little apparent difference between those with and without CAD in regard to family history of premature CAD. However, not all studies found such an association.[28] Such discrepancies may be related to patient selection (e.g., using family history as a criterion for angiography), the high prevalence of CAD in American society, or other biases.[28]

We found Lp(a) levels to be higher in those with than without CAD. However, unlike previous reports,[2,10] this trend did not reach statistical significance. These differences do not appear to be due to our younger population, because Dahlen et al[10] found that Lp(a) was a better predictor in younger (aged <55 years) than older men. We did find (data not presented) a subgroup of cases with premature CAD and normal lipoprotein profiles who had increased Lp(a) levels.

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Prognostic Importance of Quantitative Analysis of Coronary Cineangiograms

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Many studies have shown the prognostic value of angiographic data, but few have examined quantitative parameters of wall motion and shape or coronary stenosis severity. To determine whether these parameters have prognostic importance, baseline angiograms of 283 patients with up to 11.2 years (mean 8.3) of follow-up were quantitated. Event-free survival curves were constructed using log-rank testing. These indexes were also considered in 2 predictive models (Cox regression models): 1 with ("clinical") and 1 without ("quantitative") subjective angiographic analysis and clinical information. Regional shape (anterior and inferior walls) and motion (anterior wall only) indexes were predictive of event-free survival when considered singly. But these parameters were not of independent prognostic importance in the regression models. The most important independent parameters in the quantitative model for predicting overall cardiac mortality or an initial lethal cardiac event were the ejection fraction and the percent diameter narrowing of each major coronary artery. Myocardial infarction was predicted by the percent diameter stenosis of the left main and left anterior descending arteries but not the ejection fraction. In the clinical model, the factors of overriding prognostic importance were the ejection fraction and the subjective determination of the number of vessels involved with "significant" stenoses. Quantitative coronary arteriography still contributed independent prognostic value. Thus, quantification of the ejection fraction and severity of coronary lesions were of independent, prognostic importance, whereas indexes of regional function and shape were not.

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The need for quantitative and reproducible measurements of global and regional ventricular function and coronary lesion severity is unquestioned in research arenas because visual estimates are highly variable.[1] Although numerous articles have demonstrated the prognostic importance of a quantitative measure of the ejection fraction as well as some subjectively determined measures of wall motion and stenosis severity,[2–11] none have determined whether quantitative methods for assessing stenosis severity, wall motion or wall shape have independent prognostic importance. Thus, we set out to determine the prognostic importance of quantitative measures of regional wall motion, wall shape and percent diameter stenosis measurements.

METHODS

Cineangiograms of 296 patients were randomly selected by investigators at the Montreal Heart Institute from studies of 3,566 patients in the Coronary Artery Surgery Study (CASS) Registry.[12] Some patients had follow-up data up to 11.2 years (mean follow-up 8.3 years in the entire group). Clinical information was collated on patient characteristics (sex, age, prior myocardial infarction, bypass surgery or angioplasty, number of diseased vessels, location of stenoses). The number of diseased vessels was determined by the original CASS investigators who considered disease to be present when a visually apparent stenosis estimated to be ≥50% was detected.

Cineangiograms were delivered to the Ann Arbor Veterans Administration Medical Center for quantitative analysis using previously developed and validated methods. Cineangiograms were displayed on a Vanguard XR15 Projector interfaced via a video chain to an ADAC 4100C Digital Image Processing Computer (Milpitas, California). Poorly opacified left ventriculograms or studies lacking a non-postectopic beat were excluded from ventricular analysis (13 cases). The largest (end-diastolic) and smallest (end-systolic) ventricular images in the right anterior oblique projection were traced and digitized in a 256 × 256 matrix and stored. Global ejection fraction was measured using the area-length method.[13] Volumes were not measured due to absence of routinely available calibration grids.

Regional wall motion was calculated using the centerline method developed at the University of Washington and previously described in detail.[14] Briefly, a centerline is drawn midway between the end-diastolic and end-systolic outlines, 100 chords are determined perpendicular to this line and the resultant chord lengths are expressed as a fraction of the end-diastolic silhouette length. These values are then normalized by comparison to regional fractional shortening results of a normal

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population and expressed in standard deviations per chord, averaged over the anterior and inferior regions.

Similarly, regional ventricular shape was measured using a previously described and validated method developed at the University of Michigan.[15] Briefly, this method calculates the curvature at 100 points along the end-systolic silhouette. Low curvature values denote relatively straight or gently curving regions and high curvature values denote very curved areas such as is seen at the apex of a ventricular silhouette. The outward bulging of wall motion abnormalities and aneurysms causes an abnormal increase in curvature. In a fashion similar to the wall motion assessment, these curvature values are normalized by comparison to normal shape parameters of a normal population. The regional shape indexes are then reported in standard deviations per point, averaged over the anterior and inferior regions. The optimal threshold values for optimizing sensitivity and specificity of these 2 regional analysis programs have been previously determined at the University of Michigan.[15] Optimal concordance between visual and quantitative analysis of wall motion was achieved by using a critical value of −1.1 standard deviations/chord to distinguish between normal or abnormal motion. For shape abnormalities, the critical value was −0.4 standard deviations/point. Therefore, all wall motion and shape results were normalized by these previously determined values so that the numerical results could be more easily compared. The wall motion and wall shape parameters are, therefore, reported in "critical value" units.

The most severe focal lesion in each involved vascular territory designated by the CASS investigators was subjected to quantitative analysis using a previously described and validated method developed at the University of Michigan.[16] The projection showing the lesion in its most severe perspective and without overlapping side branches was digitized, stored and analyzed. Briefly, the arterial segment and lesion of interest were digitized using 2.4:1 optical magnification into a 512 × 512 image matrix and then magnified ×2 by bilinear interpolation. Density profiles perpendicular to a centerline along the longitudinal axis of the segment were analyzed to determine the first and second derivatives of the density profiles. Initial edge points were selected at 75% of the distance between the second and first derivative locations (i.e., weighted toward the location of the first derivative). These points were automatically examined for spatial continuity. Points that were not within a 4 pixel distance of neighboring edge points were eliminated automatically and replaced by interpolating between edge points on either side of the eliminated point. After this automated process, manual editing of the edge was performed when necessary to ensure accurate contour detection. Percent diameter stenosis was calculated by comparing the minimal diameter to the average diameter of a normal, proximal segment. Normal and occluded vessels were designated as having 0 and 100% diameter stenoses respectively. Absolute measures of lumen size were not recorded owing to lack of information about angiographic catheter size.

Over the term of follow-up, the following complications were recorded: unstable angina, myocardial infarction, congestive heart failure, arrhythmias, syncope, cardiogenic shock, peripheral emboli, stroke and death as well as the cause of death, and need for bypass surgery or angioplasty.

TABLE I Baseline Characteristics of the Study Group (n = 283)

Men/women	243/40
Age (years)	51 ± 8
Previous myocardial infarction	184
No. of coronary arteries narrowed ≥ 50% in diameter	
0	4
1	85
2	98
3	96
Location of narrowings	
Left main	4
Left anterior descending	216
Circumflex	162
Right	189
Ejection fraction (%)	52 ± 15
Wall motion (critical values)	
Anterior	−1.73 ± 0.99
Inferior	−1.87 ± 1.01
Wall shape (critical values)	
Anterior	−3.20 ± 2.73
Inferior	−1.46 ± 2.63

Continuous data presented as mean ± standard deviation.

Kaplan-Meier event-free curves were calculated for groups with ejection fractions below 55 and ≥55%, anterior and inferior shape or wall motion indexes ≤−2 and >−2 critical values, and percent diameter stenosis of <70 and ≥70% of the left anterior descending, circumflex and right coronary vascular distributions.[17] Bonferroni adjusted log-rank tests were used to determine the time at which differences in event-free survival curves occurred.[18] A Cox regression model was used to determine independent predictors of adverse events.[19] Two specific models were tested. The first, termed the "quantitative model" incorporated only quantitative parameters of ejection fraction, wall motion, wall shape and stenosis severity. The second, termed the "clinical model" incorporated the quantitative parameters as well as the following clinical information: sex, age, prior infarction, number of significantly stenotic vessels by visual analysis (zero, 1-, 2- or 3-vessel disease) or the presence of a stenosis considered to be ≥50% by visual analysis of the left main, left anterior descending, circumflex or right coronary arteries. These models were tested for the prediction of cardiac death at any time during follow-up. In a separate analysis we determined predictors of an initial major cardiac event causing death, and an initial fatal or nonfatal myocardial infarction. In this analysis, we considered the occurrence of arrhythmias, heart failure and unstable angina as adverse events that were likely to have initiated therapies with the potential of altering the patients' prognosis. Similarly, the occurrence of bypass surgery or angioplasty was considered an adverse event because these therapies may have altered subsequent long-term survival or the occurrence of subsequent events, or both. These patients were therefore excluded in the analysis of an initial major cardiac event causing death, and an initial fatal or nonfatal

myocardial infarction to avoid the potential confounding effects of therapy.

RESULTS

Clinical characteristics: Of the original 296 studies, complete angiographic data were obtained in 283. Table I summarizes characteristics of the study group. At entry, ages ranged from 30 to 68 years, and ejection fractions ranged between 6 and 80%. When visually identified and quantitated, the least severe left main, left anterior descending, circumflex and right coronary lesions were 50, 41, 41 and 43%, respectively. The most severe left main stenosis was 75%, whereas in the other territories total occlusions occurred. The average severity of the quantified lesions were as follows: left main (n = 4), 61 ± 15%; LAD (n = 212), 81 ± 18; circumflex (n = 161), 82 ± 17%; and right coronary artery (n = 185), 86 ± 18%. Despite a normal mean ejection fraction in this population, mean regional wall motion and shape indexes were abnormal, reflecting the high proportion of patients with prior infarctions (184 of 283). In 6 cases, the exact timing of the first significant cardiac event was unknown. Therefore, all subsequent statistical analyses were based on 277 cases. Quantitative cineangiographic findings in these patients are further summarized in Table II. One hundred forty-three of the 277 cases had ejection fractions ≥55%.

TABLE II Number of Patients with Designated Quantitative Index (n = 277)

Artery	Visually Insignificant	Quantitative Diameter Stenosis	
		<70%	≥70%
Left main	273	3	1
Left anterior descending	65	68	144
Circumflex	116	50	111
Right	92	45	140

	>−2 Critical Values		≤−2 Critical Values
Anterior motion	174		103
Inferior motion	148		129
Anterior shape	86		191
Inferior shape	140		137
	≥55%	31–54%	≤30%
Ejection fraction	143	111	23

For purposes of this study, stroke (16 events) and peripheral emboli (3 events) were considered noncardiac events. One hundred two patients had an event-free follow-up. In the remaining patients, the most frequent

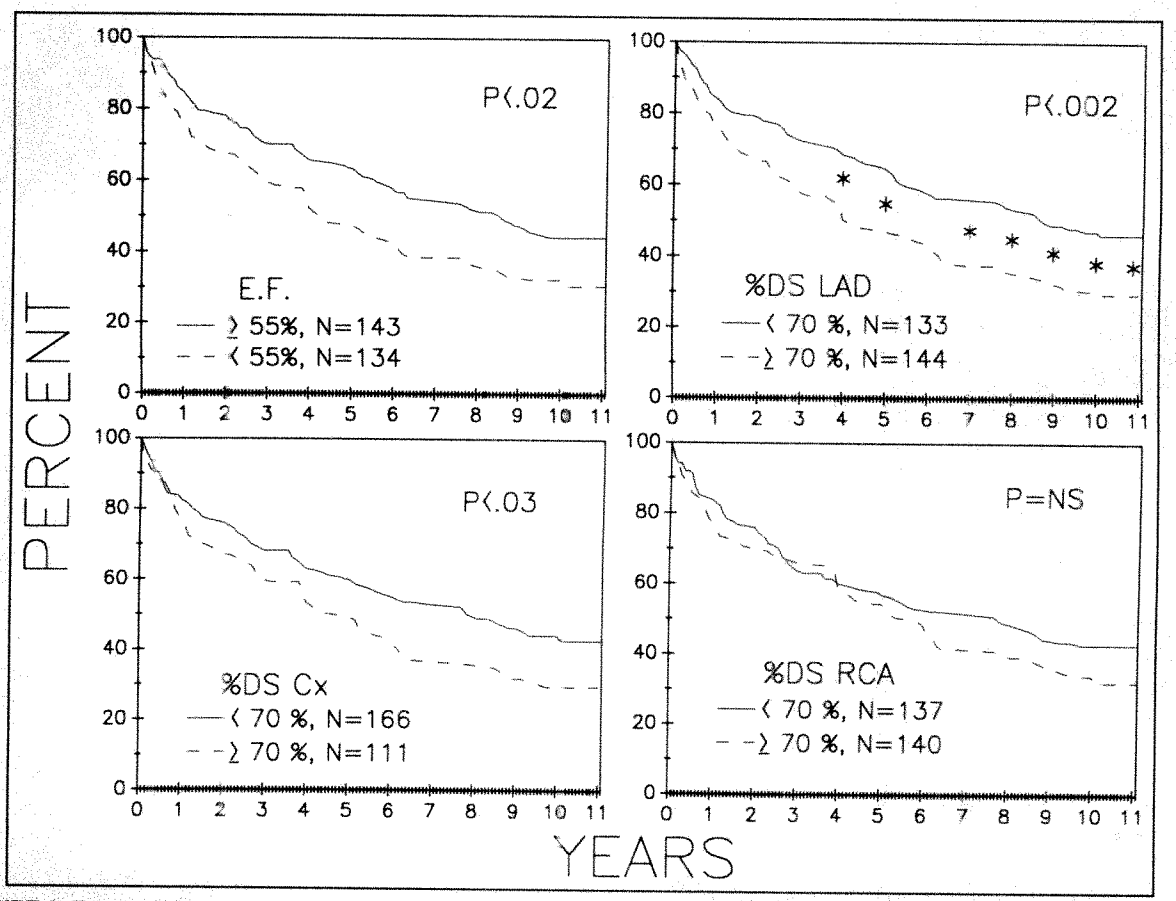


FIGURE 1. Event-free survival curves were constructed for groups of patients having normal or abnormal quantitative indexes of ejection fraction (E.F.) and percent diameter stenosis (DS) of the left anterior descending (LAD), circumflex (Cx) and right coronary (RCA) arterial beds. N refers to the number of patients with the quantitative index value at the time of the baseline angiogram. The *y axis* designates the percent of the original number of patients with event-free survival. The *x axis* is given in years. Significant overall differences are designated by the p values which are based on log-rank tests. *Symbols between curves* designate specific time points when the curves are statistically different based on Bonferroni adjustments of the log-rank test. NS = not significant; *p <0.05.

event was the onset of unstable angina in 63 patients (85 occurrences) followed by bypass surgery in 74 patients (77 occurrences) and myocardial infarction in 53 (73 occurrences). Congestive heart failure events were documented 44 times. Sudden death occurred in 25 patients. Significant arrhythmias excluding ventricular tachycardia were noted on 14 occasions and there were 5 episodes of ventricular tachycardia. Cardiogenic shock was noted 13 times. A single percutaneous coronary angioplasty reflects the emergence of the technique after the time of patient enrollment and during the course of the follow-up.

In addition to the 25 sudden deaths, there were 19 fatal myocardial infarctions (14 of which were the initial event after angiography), 7 deaths due to congestive heart failure, 6 deaths ascribed to cardiogenic shock and 2 ascribed to ventricular tachycardia. Stroke accounted for 7 deaths. In 18 cases the cause of death was not specified.

Event-free survival curves were constructed for the quantitative indexes and are demonstrated in Figures 1 and 2. The event-free survival curves were significantly different with respect to each of the quantitative parameters except in the case of inferior wall motion, and percent diameter stenosis of the right coronary artery. Significant overall differences in the event-free survival curves ($p < 0.02$) between patients with and without a normal ejection fraction (≥55%) were found, but these curves were not significantly different at any specific time point during the follow-up period. The curves based on anterior wall motion were also significantly different ($p < 0.003$) and, in contrast to the ejection fraction curves, diverged significantly from the fourth year to the end of the follow-up period. Anterior shape abnormalities were also associated with a worse, overall event-free survival ($p < 0.004$) and the curves were specifically divergent from the third year on. Inferior wall shape abnormalities also imparted a worse, overall event-free survival ($p < 0.007$), but the curves did not diverge significantly at any specific time except at the end of the follow-up period. Patients with left anterior descending territory stenoses that were <70% had a better event-free survival than those with more severe stenoses ($p < 0.002$). These curves diverged significantly from the fourth year on, except in year 6 when the curves did not quite reach statistically significant differences. Patients with stenoses of the circumflex that were <70% also had a better event-free survival ($p < 0.03$), but these curves were not statistically divergent at any specific time point. There were 59 cardiac deaths occurring during the entire follow-up period, and 37 of these deaths were in fact the initial cardiac event during follow-up. Myocardial infarction was the initial significant cardiac event during follow-up in 42 cases and 14 of these were fatal. In the "quantitative" model (Table III), the ejection fraction was of overriding importance in predicting overall cardiac death and an initial, lethal cardiac event. However, all of the quantitative percent

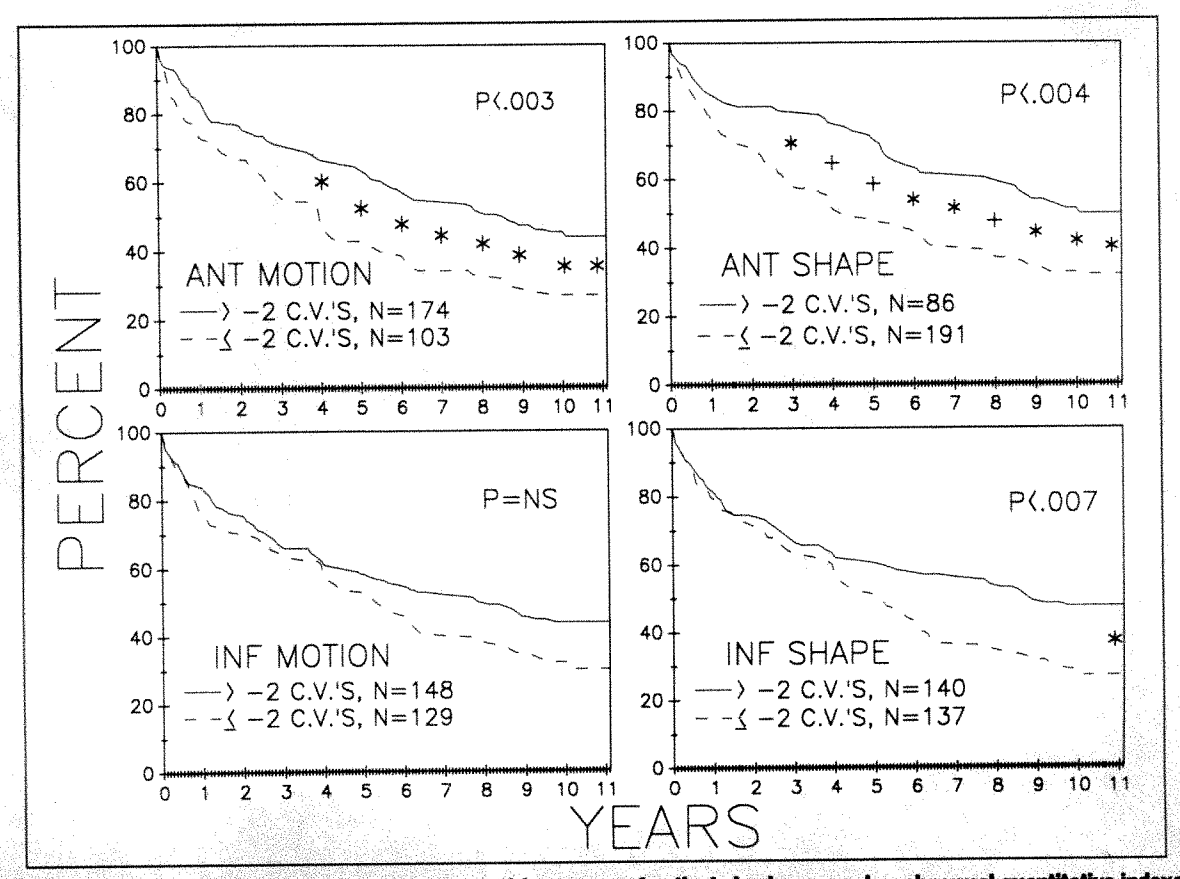


FIGURE 2. Event-free survival curves were constructed for groups of patients having normal or abnormal quantitative indexes of regional wall motion or regional shape on their baseline ventriculogram. ANT = anterior; INF = inferior; C.V.'S = critical values; +p <0.01; other abbreviations and format as in Figure 1.

TABLE III Summary of Factors Predicting Clinical Outcomes, Ranked in Order of Importance, for the Quantitative Model

Parameter	Coefficient	p Value
Cardiac death		
Ejection fraction	2.82	0.0001
% diameter stenosis:		
Circumflex	1.51	0.005
Left main	4.06	0.03
Left anterior descending	1.52	0.02
Right	1.42	0.02
Initial lethal cardiac event		
Ejection fraction	2.56	0.00001
% diameter stenosis:		
Left anterior descending	2.16	0.0001
Right	1.58	0.02
Circumflex	1.54	0.03
Left main	3.81	0.04
Myocardial infarction		
% diameter stenosis:		
Left main	4.11	0.04
Left anterior descending	1.48	0.04

diameter stenosis variables were also independently predictive. In contrast, none of the wall function indexes was predictive. Myocardial infarction was predicted by the percent diameter stenosis of left main and left anterior descending lesions but not the ejection fraction.

Results of the "clinical" predictive model demonstrated the overriding importance of the quantitated ejection fraction in predicting overall cardiac death (coefficient = 3.08, $p < 0.00001$), followed by the number of vessels diseased (coefficient = 2.03, $p < 0.0001$) and the patients' age (coefficient = 1.05, $p < 0.009$). An initial, lethal cardiac event was predicted, in order of importance, by the ejection fraction, the number of vessels diseased and the quantitative percent diameter stenosis of the left anterior descending artery (coefficients = 2.78, 2.16, 1.69, $p < 0.00001$, 0.0006, 0.05, respectively). Myocardial infarction was predicted by both the qualitative presence of a significant stenosis in the left anterior descending artery (coefficient = 3.88, $p < 0.002$) and the quantitative percent diameter stenosis of the left main artery (coefficient = 3.79, $p < 0.05$).

DISCUSSION

Many prior analyses have shown the prognostic importance of the quantitative ejection fraction, but the purported value or lack of value of other parameters of regional function and stenosis severity were uniformly based on qualitative assessments.[3-12] This study was motivated by a desire to put into perspective several of the currently available quantification methods that are applied to cineangiograms and to determine whether such parameters have prognostic power. We assessed this in a population with well-defined, long term, clinical follow-up. Our a priori expectation was that sophisticated parameters of ventricular function and shape would be of overriding clinical importance and that quantitative coronary arteriography would provide little, if any, prognostic power. But the results were quite different. In general, the simple ejection fraction remained the prime determinant of most cardiac syndromes, and sophisticated measures of regional wall motion and shape were not of independent prognostic value. Surprisingly, quantitative coronary arteriography was of independent prognostic value in both the clinical and quantitative regression models.

Groups dichotomized with respect to most quantitative parameters showed significant differences in event-free survival over the decade of follow-up. Exceptions occurred in the case of percent diameter stenosis of the right coronary artery and inferior wall motion. The most highly divergent curves were associated with anterior shape analysis, anterior wall motion analysis and percent diameter stenosis of the left anterior descending coronary artery territory.

The Cox regression models, however, serve to put these univariate results into perspective by demonstrating the overriding importance of the ejection fraction.[5-10,20] Despite this, other factors were also of independent, prognostic importance. These were generally not related to more detailed or sophisticated measures of regional function or shape and this is almost certainly because these parameters are highly correlated with the less complex ejection fraction calculation. Instead, the quantitative measures of percent diameter stenosis, especially of the left anterior descending coronary bed or the left main coronary artery were the parameters that contributed additional and independent prognostic value. This was particularly the case when considering initial, lethal cardiac events or myocardial infarction.

A recent study has made the provocative observation that severe lesions are often not the sites of subsequent occlusion and causation of myocardial infarctions.[21] Others have shown an association between lesion severity and infarction.[22] The current study suggests that over a long follow-up period, the quantitative severity of coronary lesions, especially of the left main or left anterior descending artery, is indeed predictive of infarction. Whether these severe lesions are actually the sites of occlusion leading to infarction cannot be established from the current study because follow-up angiograms were not available. One can only conclude that the presence of severe lesions portends a higher risk of subsequent infarction.

Regional function and shape indexes are often used in studies of thrombolysis. These studies often focus on segmental effects and minimize attention to either arteriographic findings or overall ejection fraction measurements. However, because these parameters were eliminated in both the clinical and quantitative models, one must question the use of isolated measures of wall function as surrogate end points in many clinical trials. Our results suggest that these parameters should not be evaluated separately from the quantitative coronary arteriographic results and that the overall ejection fraction results in such studies should never be deemphasized.[23]

The clinical model was chosen because it approximates the cognitive aspects of clinical decision making that take into account many factors influencing the interpretation of test results.[24] Thus, this model included patient age, sex, the presence of prior infarction and subjective assessments of the number of vessels with "significant" stenoses, and their location. These are not

the only factors and perhaps not even the main factors that a practicing cardiologist would use to make an overall clinical assessment of risk or a clinical decision regarding therapy. For example, results of exercise testing and especially functional radionuclide studies commonly sway clinical decisions, and such results were not incorporated into this study. In this context, although the ejection fraction and the number of diseased vessels are the most consistent and important determinants of adverse clinical outcomes, quantitative coronary arteriography was of independent, prognostic power, whereas wall motion and shape analyses were not.

The percent diameter stenosis parameter, even measured meticulously, has been roundly criticized in recent years based on (1) recognition of the diffuse nature of atherosclerosis and the resultant difficulty in selecting normal reference diameters[25]; (2) the fact that such measurements do not take into account other important morphologic features such as length or entrance and exit angles[26]; (3) the realization that many stenoses are eccentric and cannot be accurately represented by a single plane measurement[25]; (4) the new knowledge that remodeling and dilatation of vessels occurs in response to atherosclerosis[27]; and (5) the imprecise relation between this parameter and other directly measured indexes of functional stenosis severity.[28,29] Whereas all of these arguments are cogent, this study suggests that percent diameter stenosis, much like the ejection fraction with its well-recognized limitations, is still of tremendous prognostic importance and is an appropriate parameter upon which to base routine clinical judgments.[24] Much greater experience and long-term follow-up analyses, such as the one presented in this study, will need to be undertaken with the alternative proposed indexes of stenosis severity before replacing the simple quantification of percent diameter stenosis.

This study should not be interpreted to imply any potential "superiority" of quantitative arteriography over subjective stenosis assessment. However, neither should the visual assessment of presence and severity of stenoses by the original CASS investigators be equated with the more casual day-to-day assessments used in practice. Nevertheless, because only the quantitative methods are associated with a high degree of reproducibility, and because these parameters have now been shown by this study to have prognostic importance, one may conclude that such quantitative measures would be suitable not solely for research purposes, but also for clinical decision-making if the indexes could be obtained expeditiously and within practical constraints. This study therefore provides a clinically relevant reason, beyond merely that of enhanced reproducibility, to promote the development of quantitative and verifiable methods that can be used easily in clinical practice.[30]

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Supraventricular Tachycardia Mechanisms and Their Age Distribution in Pediatric Patients

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To better define the natural history of supraventricular tachycardia (SVT) in young patients, age distribution of SVT mechanisms was examined in 137 infants, children and adolescents. Patients with a history of cardiac surgery or neuromuscular diseases were excluded. An electrophysiologic study was performed in each patient: transesophageal (110 patients) or transvenous (14 patients) or both (13 patients). Mechanisms were classified as SVT using accessory atrioventricular (AV) connection (SVT using accessory connection, including orthodromic and antidromic reciprocating tachycardia), primary atrial tachycardia (including chaotic, automatic and reentrant atrial tachycardia), and tachycardia due to reentry within the AV node. SVT using accessory connection occurred in 100 of 137 patients (73%) and was the most prevalent mechanism. Primary atrial tachycardia and reentry within the AV node were present in 19 of 137 (14%) and 18 of 137 (13%) patients, respectively. Using a multinomial logit model, relative probabilities for tachycardia mechanisms for 5 age groups — prenatal, <1, 1 to 5, 6 to 10 and >10 years — were determined. Primary atrial tachycardia (11 to 16%) and SVT using accessory connection (58 to 84%) appeared throughout infancy, childhood and adolescence. On the other hand, tachycardia due to reentry within the AV node (0 to 31%) rarely appeared before age 2 years. Mechanisms of SVT appear to have age-dependent distributions. SVT using accessory connection is the most common mechanism in young patients. We speculate that the propensity to tachycardia due to reentry within the AV node occurs during postnatal development.

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Supraventricular tachycardia (SVT) or paroxysmal atrial tachycardia, as it is also known, is a common abnormality of heart rhythm in infants, children and adolescents. In the past 2 decades, much has been learned regarding electrocardiographic and electrophysiologic features of SVT mechanisms.[1–9] It is now known that tachycardias requiring participation of both ventricular and supraventricular tissues have been termed SVT. For example, in SVT using an accessory atrioventricular (AV) connection, both atria and ventricles are essential for continuation of tachycardia. On the other hand, in SVT thought to result from reentry within the AV node, the precise role of the atria and ventricles in maintaining tachycardia is unclear. Finally, there are SVT types (e.g., ectopic atrial tachycardia), where the atria are the principal site of the electrophysiologic disturbance; these types have been termed atrial[8] or primary atrial tachycardias.[6]

It is generally agreed that accessory AV connections used in certain SVT types are developmental anomalies. However, much less is known of the developmental aspects of either primary atrial tachycardias or tachycardias due to reentry within the AV node. We hypothesized that SVT mechanisms are age-dependent. To test this hypothesis, we evaluated the frequency and age distribution of SVT mechanisms in pediatric patients.

METHODS

Patients: The records of electrophysiologic studies performed from July 1986 through January 1991 on 137 patients with electrocardiographically documented SVT were reviewed. There were 57 female and 80 male patients. Patients with electrocardiographic documented tachycardia with prolonged QRS duration and AV dissociation, as might be seen in patients with ventricular tachycardia or tachycardia using a nodoventricular connection, were not included.[10] Additionally, patients who had undergone open heart surgery, as well as patients known to have neuromuscular diseases were not included. However, we included 8 patients with nonsurgically treated congenital heart disease and 1 infant of a diabetic mother with hypertrophic cardiomyopathy.

Definition and diagnosis: Based on tachycardia characteristics, patients were divided into 3 groups: primary atrial tachycardia, SVT using accessory AV connection, and tachycardia due to reentry within the AV node. The classification of an SVT mechanism was made independently by 3 of the authors. SVT classification was based on analysis of the initiation method of SVT, electrophysiologic features, and response to pharmacologic agents or maneuvers that impaired AV or myocardial conduction.

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Primary atrial tachycardia[6] is that in which the primary electrophysiologic disturbance is restricted to atrial tissue, and it includes atrial ectopic tachycardia, intraatrial reentry tachycardia, atrial flutter and chaotic atrial tachycardia.[11] Electrophysiologic characterization was based on the presence or absence of 2° block during tachycardia, whether tachycardia could be induced or terminated by pacing, and the response to pharmacologic agents (e.g., adenosine) or maneuvers (e.g., Valsalva) that impaired AV conduction.

SVT using accessory connection includes orthodromic and antidromic reciprocating tachycardia, and the permanent form of junctional reciprocating tachycardia. Orthodromic reciprocating tachycardia is defined as a tachycardia with normal QRS, no evidence of AV dissociation, anterograde conduction over the AV node, and retrograde conduction through an accessory connection. During tachycardia, the ventriculoatrial interval, as measured from the onset of QRS to the rapid deflection of the atrial component of the transesophageal electrocardiogram, is >70 ms.[12,13] Prolongation of the cycle length or ventriculoatrial interval in the presence of bundle branch block ipsilateral to the accessory connection supported the diagnosis.[14] In addition, during transvenous electrophysiologic study, the presence of eccentric atrial activation and atrial preexcitation by ventricular extrastimuli at a time when the His bundle was refractory[15] supported the diagnosis of orthodromic reciprocating tachycardia. Antidromic reciprocating tachycardia shows a prolonged QRS duration with conduction anterograde over an accessory connection and retrograde conduction via either the AV node or an additional accessory connection; the QRS morphology resembles that present with preexcitation and can be duplicated with atrial pacing at a comparable rate. The permanent form of junctional reciprocating tachycardia is an incessant tachycardia considered to be a special case of orthodromic reciprocating tachycardia with anterograde conduction over the AV node and retrograde conduction over a septal accessory connection with decremental conduction properties[16]; the ventriculoatrial interval is prolonged, and there is no evidence of cycle length change with functional bundle branch block.

The diagnosis of tachycardia due to reentry within the AV node is made by excluding SVT using accessory connection and primary atrial tachycardia. In both typical (common) and atypical (uncommon) types, the critical elements of the reentry circuit are thought to be restricted to the region of the AV junction.[4,8,9,12,13] During the typical type, the ventriculoatrial interval during tachycardia is short whether measured during transvenous[12] or transesophageal[13] electrophysiologic study. The atypical form in association with longer ventriculoatrial intervals occurs less often.[9,12,13]

Electrophysiologic study: An electrophysiologic study was performed in each patient. Studies were performed in the postabsorptive and antiarrhythmic drug-free state. Before study, parental consent was obtained. During study, sedation was maintained using meperidine (1 mg/kg), promethazine (1 mg/kg), morphine (0.1 mg/kg) or midazolam (0.1 mg/kg) as needed. A transesophageal study was performed in 110 patients (2 days to 19 years), whereas in 14 patients (25 months to 17 years) a transvenous electrophysiologic study was performed. Both techniques were eventually performed in 13 patients (5 months to 19 years).

Transesophageal electrophysiologic study: The techniques for transesophageal pacing and electrocardiographic recording have been previously described.[17] A bipolar esophageal and 3 surface electrocardiograms were recorded using a strip-chart recorder at a paper speed of 50 and 100 mm/s. Anterograde conduction and refractory characteristics were assessed. During tachycardia, the esophageal electrocardiogram was recorded and special attention was paid to the atrial and ventricular cycle lengths and to the AV relationship. When appropriate, the ventriculoatrial interval was measured from the onset of QRS to the rapid deflection of the atrial waveform.

Transvenous electrophysiologic study: The techniques for transvenous electrophysiologic study using 3 or 4 percutaneously inserted quadripolar electrode catheters have been previously described.[18] Intracardiac electrograms were simultaneously recorded with a 3-lead electrocardiogram on a strip-chart recorder as in the transesophageal study. Anterograde and retrograde conduction and refractory characteristics were assessed, and atrial mapping procedure was performed at multiple sites in the right atrium and coronary sinus during both tachycardia and right ventricular pacing. Premature extrastimuli were administered in the right ventricular apex during tachycardia.

Pacing and pharmacologic maneuvers: Anterograde and retrograde conduction were assessed by pacing at cycle lengths ranging from slightly faster than the sinus cycle length to those producing 2° AV block. Refractory characteristics were assessed using the extrastimulus technique. To induce tachycardia, 1 or 2 atrial extrastimuli at progressively closer coupling intervals were introduced into normal sinus and paced rhythms, incremental atrial pacing to 2° AV block; burst pacing at cycle lengths similar to those producing AV block were performed. If tachycardia was not initiated under basal conditions, isoproterenol (0.02, 0.05, and 0.1 μg/kg/min to a maximal rate of 4 μg/min) was infused and the pacing protocol was repeated. If tachycardia was not initiated, atropine (0.04 mg/kg) was infused and the protocol was repeated.

Because the rationale for electrophysiologic study was to establish an electrophysiologic diagnosis and define therapeutic alternatives, the effects of the following intravenous medications were assessed during many studies: edrophonium (0.15 mg/kg), verapamil (0.15 mg/kg), propranolol (0.2 mg/kg), procainamide (15 mg/kg over 15 minutes) and adenosine (maximum 300 μg/kg). Additionally, in many patients the response to Valsalva maneuver was assessed.

STATISTICS

A multinomial logit model was used to evaluate the pattern of age distribution by SVT mechanism. Patients were divided into 5 age groups: prenatal, <1, 1 to 5, 6 to 10, and >10 years. For each age group, frequency estimates were generated for each tachycardia type and

conditional probabilities were computed from these frequency estimates. Models were examined to test for linear and quadratic effects. The difference in likelihood ratio statistics for logit models as well as comparing parameter estimates to their standard errors was used to determine the best model. The Kruskal-Wallis nonparametric test was used to compare the time interval between symptom onset and electrophysiologic study. Analyses were performed using SPSS PC+ (version 4.0).

RESULTS

An SVT mechanism was determined for each patient. In 135 of 137 patients (98%), there was uniform agreement between the 3 primary reviewers. In 2 patients, there was disagreement between the primary reviewers, and these 2 patients were classified by the majority opinion. SVT using accessory connection occurred in 100 of 137 patients (73%). Primary atrial tachycardia occurred in 19 of 137 patients, (14%) and tachycardia due to reentry within the AV node occurred in 18 of 137 patients (13%). SVT was first reported at a median age of 0.5 years (prenatal to 19 years); SVT was first detected at age <1 year in 78 patients (58%). SVT was recognized in utero in 21 of these 78 patients. Electrophysiologic study was performed at a median age of 4.3 years (1 day to 21 years), and in 51 of 137 patients (37%) the evaluation was performed at age <1 year.

Primary atrial tachycardia: Primary atrial tachycardia was present in 19 patients (8 female, 11 male). Tachycardia was present in 11 infants, and 4 of 11 infants had been diagnosed in utero. Electrophysiologic study was performed during the first year of life in 11 patients.

Tachycardia due to reentry within the atrioventricular node: This mechanism was present in 18 patients (9 female, 9 male). A classification difficulty was posed by 2 patients: a 7-year-old girl with block "in a lower final common pathway" associated with the typical form,[9] and a 13-year-old girl thought to have atypical form. The typical form was present in 17 patients. In 3 patients, tachycardia was first reported in infancy, but none was detected in utero. No patient had electrophysiologic study during the first year of life.

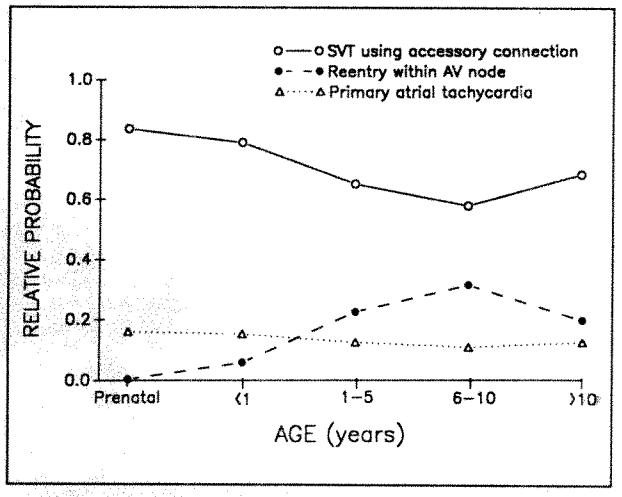


FIGURE 1. Graphic representation of the probability estimate of tachycardia type by age for supraventricular tachycardia (SVT) using accessory connection, tachycardia due to reentry within the atrioventricular (AV) node, and primary atrial tachycardia.

Supraventricular tachycardia using accessory connection: SVT using accessory connection was present in 100 patients (40 females, 60 males). Tachycardia was present in 64 infants and in 17 of 64 infants the diagnosis was in utero. Electrophysiologic study was performed in 40 patients during the first year of life. Ventricular preexcitation was present in 48 patients (48%).

Relation of tachycardia mechanisms with age: With use of a multinomial logit model, probabilities for tachycardia mechanisms by age were determined (Figure 1). Both the likelihood ratio chi-square statistic and the size of the parameter estimate, relative to the standard error indicated the quadratic model fit better than the linear model. SVT using accessory connection occured more often than the other 2 mechanisms (58 to 84%). Primary atrial tachycardia was relatively uncommon (11 to 16%) but appeared throughout infancy, childhood and adolescence. However, tachycardia due to reentry within the AV node (0 to 31%) rarely appeared before age 2 years.

Age at symptoms and age at study: The median interval between the age at symptom onset and the age at electrophysiologic study was 1.1 years (range 0.0 to 17.5). In 47% of patients, the interval was <1 year: 2 of 18 patients (11%) with tachycardia due to reentry within the AV node, in 14 of 19 patients (74%) with primary atrial tachycardia, and in 48 of 100 patients (48%) with SVT using accessory connection. Thus, patients with either SVT using accessory connection or primary atrial tachycardia tended to undergo electrophysiologic study within 1 year of symptom onset, whereas patients with tachycardia due to reentry within the AV node tended to undergo electrophysiology study >1 year after symptom onset ($p < 0.05$).

Comparison of transesophageal and transvenous electrophysiologic study: Both transvenous and transesophageal electrophysiologic studies were performed in 13 patients. Transesophageal study was performed initially, but transvenous study was eventually performed to evaluate suitability of ablation, antitachycardia pacemaker and investigational drug options. SVT using accessory connection was present in 10 patients, including orthodromic (6 patients), orthodromic and antidromic (1 patient), and antidromic-reciprocating tachycardia (1 patient), and permanent junctional reciprocating tachycardia (2 patients). Primary atrial tachycardia was present in 3 patients: atrial ectopic (1 patient) and intraatrial reentry (2 patients) tachycardia. In all 13 patients, the mechanisms of SVT determined by the 2 studies were identical.

Supraventricular tachycardia with associated heart disease: SVT using accessory connection was present in 9 patients with associated heart disease, including Ebstein's anomaly, scimitar syndrome, secundum atrial septal defect, primum atrial septal defect, and corrected transposition in 1 patient each and ventricular septal de-

fect in 2 patients. An infant of a diabetic mother had associated hypertrophic cardiomyopathy.

DISCUSSION

The main finding of this study in pediatric patients is that mechanisms of SVT appear to have age-dependent distributions. We grouped SVT patients into 3 major mechanisms: primary atrial tachycardia, SVT using accessory connection, and reentry within the AV node. Among the patients studied, SVT using accessory connection was the predominant mechanism (73%) of SVT, and most patients with SVT using accessory connection or primary atrial tachycardia developed symptoms before age 1 year. In contrast, tachycardia due to reentry within the AV node occurred nearly as often as primary atrial tachycardia, but no cases were detected in utero and symptoms rarely occurred before age 2 years.

In the patients we studied, SVT using accessory connection was more common than previous reports in children and adults.[1,2,8,9] Reentry within the AV node has been reported to be the most common mechanism of SVT in adults without ventricular preexcitation.[8,9,19] In our study of pediatric patients, this mechanism was more likely to occur in older children. The incidence of primary atrial tachycardia (14%) is also low compared to 21 to 34% present in previous studies in pediatric patients.[1,2]

There may be 2 reasons related to our patient selection to explain the predominance of SVT using the accessory connection. First, we were restrictive in patient selection and excluded all patients who had undergone open heart surgery or those who had neuromuscular disease which might be etiologic in the cause of SVT. These exclusion criteria may have resulted in a relative decrease in frequency of primary atrial tachycardia, which is known to be associated with these conditions.[20–23] Second, indications for study vary from center to center because there have been no generally agreed upon guidelines for either transesophageal or transvenous electrophysiology study. At our institution, transvenous study is usually reserved for patients with SVT who pose a diagnostic dilemma, or those in whom ablation, pacemaker or investigational drug therapy is considered. It is our practice to perform transesophageal studies in all pediatric patients presenting with SVT, especially when SVT is refractory to empiric antiarrhythmic therapy. This practice allowed electrophysiologic characterization of tachycardia features in many infants and young children who warranted evaluation but in whom intracardiac study would have been impractical and unwarranted.

We evaluated the age distribution of SVT mechanism both by age at symptom onset and age at time of study as a way to deal with the potential problem that a patient might have a different mechanism of tachycardia at an earlier versus later time in life. For example, an infant may have SVT using accessory connection but lose the capacity for this tachycardia during the first year of life, only to develop a propensity for tachycardia due to reentry within the AV node later in life. This possibility is supported by 2 considerations: The accessory connection may change electrophysiologic characteristics during maturation,[7,24–27] and the occurrence of tachycardia due to reentry within the AV node has been reported in patients with accessory connection.[28,29]

Study limitations: The possibility of selection bias or misclassification due to inadequate diagnostic criteria are the principal limitations of the study. Our study was limited to patients referred to a tertiary center; we estimate the indications for study at our center result in approximately 95% of patients with SVT undergoing some type of electrophysiologic study. The results of the present and previous[13] studies show that in the child and adolescent, transesophageal study can accurately determine SVT mechanisms. However, the lack of established diagnostic criteria for infants, in whom the standard multicatheter study is not feasible, poses a problem. Consequently, in the absence of an agreed-upon gold standard for infants, we relied on the classification by 3 experienced pediatric electrophysiologists.

Speculation: It was previously suggested that all infants with paroxysmal SVT may have accessory AV connections.[30] It is now generally accepted that accessory AV connections are developmental anomalies.[31] Much of the variation in prenatal and postnatal tachycardia occurrence may be explained by both developmental changes in the accessory connection[7,24] and developmental variation in the occurrence of initiating events.[32] The developmental aspects of the morphologic and functional basis of ectopic or reentrant primary atrial tachycardias in nonsurgically treated patients have been only partially described,[20,33] but based on results of the present study they may occur prenatally and postnatally throughout childhood. In the patients we evaluated, tachycardia due to reentry within the AV node occurred nearly as often as primary atrial tachycardia. However, no occurrence was detected prenatally and few cases were detected in the first year of life, suggesting an age-dependent anatomic or functional basis for tachycardia due to reentry within the AV node. Based on these considerations, we speculate that the propensity to tachycardia due to reentry within the AV node occurs during postnatal development.

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On the Mechanism of Termination and Perpetuation of Atrial Fibrillation

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In an effort to further clarify the mechanism of termination and perpetuation of atrial fibrillation (AF), the intraatrial potentials during AF induced by programmable electrical stimulation were analyzed using the concept of wavelength which represents the size of a microreentrant circuit. Thirty patients with inducible AF were divided into 2 groups: 20 patients with AF that terminated spontaneously (group 1) and 10 patients with AF that did not terminate spontaneously (group 2). Wavelength is the product of refractory period and conduction velocity. During AF, the refractory period of the local atrial tissue was considered to correlate with the mean interval between each intraatrial potential (mean ff). An inverse relation was considered present between conduction velocity of the impulse and the width of intraatrial potentials (f width). Thus, the wavelength index was defined as (mean ff)/(mean f width). Ten intraatrial potentials at the high right atrium were sampled for measurement. Group 1 had higher wavelength indexes just after the induction of AF than did group 2 (1.33 ± 0.31 vs 1.10 ± 0.05, $p < 0.05$). In group 1, the wavelength indexes were increased from the initial value to 1.49 ± 0.36 just before termination of AF ($p < 0.001$). In 3 group 2 patients, AF stopped after disopyramide was administered intravenously, whereas the wavelength indexes at the end of AF were higher than those before drug administration (1.27 ± 0.08 vs 1.16 ± 0.04, $p < 0.05$). In conclusion, prolongation of the wavelength appears to be a major determinant for termination of AF, and shorter wavelengths are necessary for perpetuation of AF.

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The mechanism of atrial fibrillation (AF) in humans remains uncertain. However, experimental and clinical studies have revealed evidence that the reentrant mechanism is involved in the genesis and maintenance of AF.[1–6] Actually, functionally determined multiple circuits altering their own shapes constantly without the involvement of a gross anatomic obstacle (leading circles) are regarded as the basis of this arrhythmia. In the leading circle-type reentry, the size of the reentrant circuit is determined by the wavelength that is the product of refractory period and conduction velocity.[7]

This basic concept had not been applied to the analysis of human AF so far because refractory periods of the local atrial tissues and conduction velocity of circulating impulses could not be identified in clinical AF. In an attempt to further elucidate the mechanism of termination and perpetuation of AF, we undertook an analysis of the intracardiac potentials of the atrium during AF in the electrophysiologic study with the newly developed wavelength index that comprised the clinically feasible parameters. This semiquantitative value, a wavelength index, was considered to represent the size of the microreentrant circuit. Furthermore, to determine whether alteration of the wavelength index contributed to the termination of AF, disopyramide was administered intravenously to patients whose AF induced by the electrical atrial stimulation did not terminate spontaneously.

METHODS

Patients: Thirty of 482 patients who underwent electrophysiologic studies between August 1982 and July 1990 in this institution were enrolled in this study. Inclusion criteria were the inducibility of AF by electrical stimulations and the absence of significant organic heart disease. Induction of AF was not a definitive purpose of the electrophysiologic study but the result of the routine stimulation protocol. Each patient had a normal thyroid function. These 30 patients were divided into 2 patient groups: group 1, 20 patients whose induced AF terminated spontaneously during the electrophysiologic study; group 2, 10 patients whose induced AF continued for >30 minutes. There were no significant differences in the mean age between groups. The study population is summarized in Table I.

Electrophysiologic study: Electrophysiologic studies were performed with the patients in the nonsedated and postabsorptive states after antiarrhythmic medications had been discontinued for ≥72 hours. Each patient gave written informed consent. We used 6F-USCI electrode catheters with a 10 mm interelectrode distance. Gener-

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TABLE I Study Population

	Group 1	Group 2
No. of patients	20	10
Mean age (year)	52 ± 11	48 ± 17
Men/women	16/4	7/3
Disease (no. of pts.)		
Sick sinus syndrome	3	1
Paroxysmal AF	8	3
AV block	0	1
Wolff-Parkinson-White syndrome	8	4
AV nodal reentrant tachycardia	1	1
Electrophysiology (ms)		
Atrial effective refractory period	202 ± 26	198 ± 29
AH interval	75 ± 16	79 ± 15
HV interval	42 ± 3	43 ± 4
Intraatrial conduction time (=PA interval in the His bundle electrogram)	41 ± 11	39 ± 6

Values are mean ± standard deviation.
AF = atrial fibrillation; AV = atrioventricular.

ally, 2 quadripolar electrodes were positioned in the high right atrium and the coronary sinus to record the adjacent electrical activity.[8] The His bundle electrogram was obtained by a tripolar electrode placed just across the tricuspid valve. The right atrium and the right ventricle were paced by bipolar electrodes. Electrocardiographic leads I, aVF and V_1 were recorded simultaneously on an 8-channel Siemens Mingograph at a standard paper speed of 100 mm/s. Programmed stimulation was performed using a square wave at twice diastolic threshold. The stimulation protocol included the extrastimulus method at basic cycle lengths of 545 and 667 ms and incremental pacings up to 260 beats/min for the right atrium or ventricle. The data from the extrastimulus method were compared in the same basic cycle length.

Wavelength index: Wavelength of the refractoriness is the product of functional refractory period and conduction velocity.[7] During AF, refractory periods of local atrial tissues and conduction velocity of the impulse cannot be determined. After AF occurred, the interval between intraatrial potentials (ff interval) and the width of intraatrial potentials (f width) were measured at the high right atrium. According to Mines,[9] a cycle length of the circuit is expressed as follows provided that there are no excitable gaps: CL = L/CV where CL, L and CV are cycle length of the circuit, anatomic length of the circuit and conduction velocity, respectively. In the leading circle-type circuit, the wavelength is equal to the anatomic length of the circle so that the cycle length is equal to the refractory period: CL = (RP · CV)/CV = RP where RP is refractory period. Thus, refractory periods of the local atrial site were evaluated by the ff interval basis. We chose the average ff interval as the representative of the refractory period instead of the shortest ff interval. As conceived in the multiple wavelet hypothesis of Moe,[2] which has recently been confirmed by the experimental work done by Allessie et al,[6] multiple circulating impulses may be passing by the recording site, a bipolar electrode in the high right atrium. Thus, we considered the average ff interval to be preferable as the correlative for refractory periods to the shortest value of ff interval. However, we considered that the conduction velocity correlated inversely with the width of intraatrial potentials. Accordingly, if impulses pass over the bipolar electrodes more slowly, the duration of the potentials will be longer. Therefore, we defined the wavelength index as: wavelength index = (mean ff interval)/(mean f width).

The mean ff interval was defined as an arithmetic averaged value of a series of 10 ff intervals sampled from the high right atrial electrogram. Though there are no isoelectric lines in the standard electrocardiogram of AF, some isoelectric portions can be seen in the intraatrial electrograms during AF. Thus, the mean f width was defined as an arithmetic mean of the durations in 10 intraatrial potentials that belonged to the above-mentioned series of electrograms.

Disopyramide administration: Disopyramide of 1.5 mg/kg was administered intravenously to 4 group 2 patients after a 30-minute continuation of AF. Intracardiac electrograms were recorded continuously for 30 minutes after drug infusion.

Statistics: Statistical analysis was performed using Student's *t* test and a paired *t* test when appropriate. A p value <0.05 was considered significant. All data were presented as mean ± standard deviation.

RESULTS

Clinical electrophysiology: Electrophysiologic features are summarized in Table I. Atrial effective refractory periods could not be compared precisely between groups 1 and 2 because such periods were undetermined because of easily occurring AF or other atrial arrhythmias in some group 1 patients and in half of the group 2 patients. However, there were no significant differences in atrial effective refractory periods between groups 1 and 2. Neither were there significant differences in the AH interval, HV interval or intraatrial conduction time

TABLE II Data Presentation

	Group 1 vs Group 2		Initial vs Termination (group 1)		Initial vs Termination (group 2/disopyramide)	
Mean ff (ms)	176 ± 23	157 ± 21 *	176 ± 23	194 ± 23 †	149 ± 30	173 ± 6
Mean f width (ms)	135 ± 18	144 ± 21	135 ± 18	133 ± 20	128 ± 27	137 ± 8
Wavelength index	1.33 ± 0.31	1.10 ± 0.05 *	1.33 ± 0.31	1.49 ± 0.36 ‡	1.15 ± 0.04	1.27 ± 0.08 *

Values are mean ± standard deviation.
*$p<0.05$; †$p<0.01$; ‡$p<0.001$.

(PA interval in the His bundle electrogram) between the groups.

Wavelength index: Data concerning wavelength indexes are presented in Table II and Figure 1. Wavelength indexes just after the onset of AF in group 1 were higher than those in group 2. On the other hand, the average ff intervals were longer in group 1 than in group 2 ($p < 0.05$) and the average f widths were somewhat shorter in group 1 than in group 2, although statistical significance was not present. In group 1, wavelength indexes increased significantly just before the termination of AF compared with the initial values ($p < 0.001$); the average ff intervals lengthened compared with the initial values ($p < 0.01$). A similar trend was observed in the wavelength indexes when AF terminated in 3 group 2 patients after intravenous administration of disopyramide. Accordingly, wavelength indexes increased just before termination of AF ($p < 0.05$); the average ff intervals were also lengthened, although not statistically significantly. In the patient whose AF did not terminate after disopyramide infusion, the arrhythmia discontinued 3 hours after the electrophysiologic study so that alteration in the wavelength index could not be estimated. Examples of electrophysiologic consequences in individual patients are shown in Figures 2, 3 and 4.

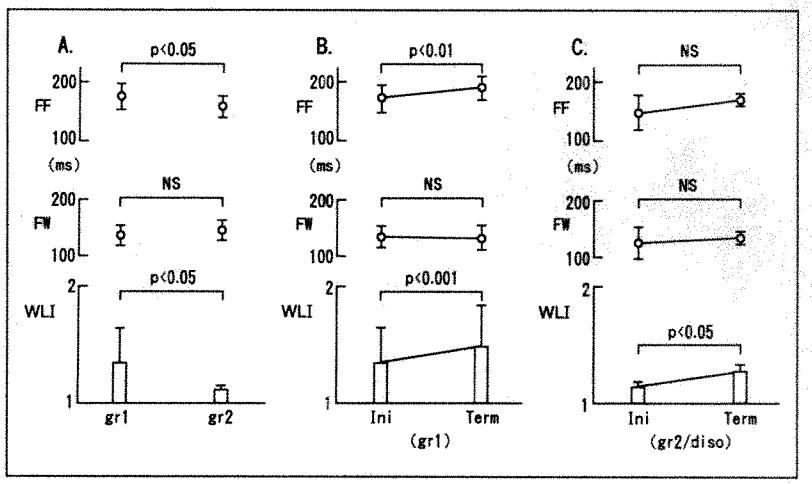


FIGURE 1. Mean ff interval (FF), mean f width (FW), and wavelength index (WLI). *A.*, comparison of the values at the onset of atrial fibrillation (AF) between group 1 (gr 1) and group 2 (gr 2); *B.*, alteration in values at the termination of AF in group 1; *C.*, alteration in values in group 2 patients to whom disopyramide was administered during AF (gr 2/diso). Individual data are presented in Table II. NS = not significant.

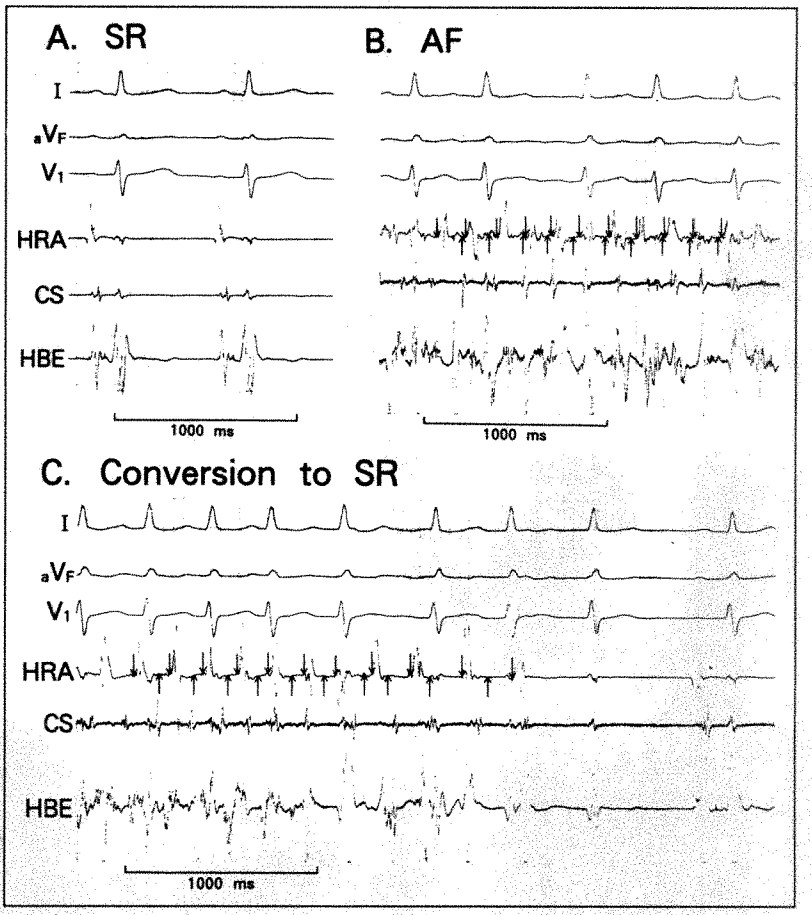


FIGURE 2. Electrophysiologic consequences in a group 1 patient with paroxysmal atrial fibrillation (AF). *A.*, intracardiac electrograms during sinus rhythm (SR); the wavelength index was altered from 1.14 (*B.*, AF) to 1.4 (*C.* just before a sinus rhythm). A neighboring ↓–↓ distance and a neighboring ↓–↑ distance stands for an ff interval and an f width, respectively. See text for details concerning the calculation of the wavelength index. CS = coronary sinus electrogram; HBE = His bundle electrogram; HRA = high right atrial electrogram.

DISCUSSION

Various studies were previously performed to clarify the mechanism underlying AF. Some studies favored an abnormal focus (foci) for the mechanism of genesis of AF.[10–12] Vagal stimulation should depress automaticities, whereas vagal stimulation usually accelerates the atrial rates of AF by shortening of the refractory periods.[13,14] At least an ectopic-focus hypothesis is not likely to account for the mechanism underlying AF maintenance. It has been increasingly evident that small reentrant circuits in the myocardial tissues constitute an important mechanism of atrial tachyarrhythmias.[1–6] In contrast, macroreentrant loops incorporating a fixed anatomic pathway contribute to the mechanism of circus movement tachycardia in the Wolff-Parkinson-White syndrome and some cases of atrial flutter.[15,16] Such kinds of arrhythmia are stable when the length of the anatomic circuit is longer than the wavelength of the electrical impulse. The difference between the anatomic length and wavelength is the excitable gap.

Recent studies supported multiple wavelets based on microreentrant circuits for the AF maintenance mechanism.[2,3,6] These microreentrant circuits do not involve a gross anatomic obstacle and are determined by elec-

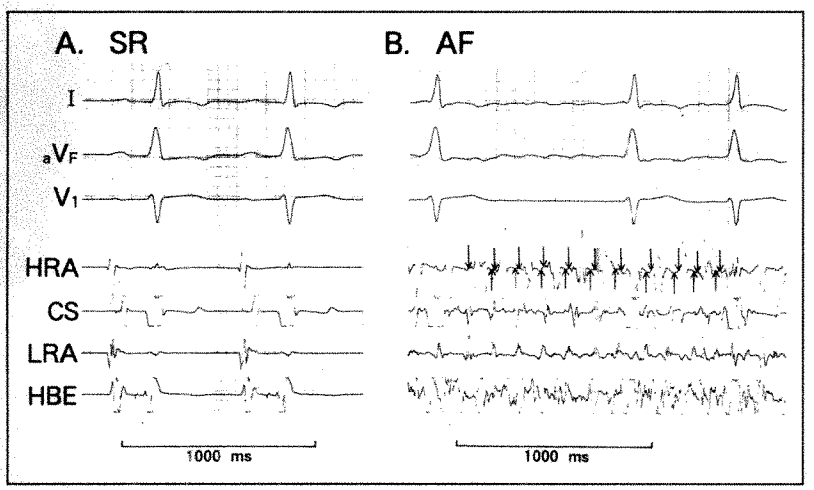


FIGURE 3. Electrophysiologic consequences in a group 2 patient with paroxysmal atrial fibrillation. *A.*, intracardiac electrograms during sinus rhythm; the wavelength index was calculated as 1.09 during atrial fibrillation *(B.)*. LRA = low right atrial electrogram; other abbreviations as in Figure 2.

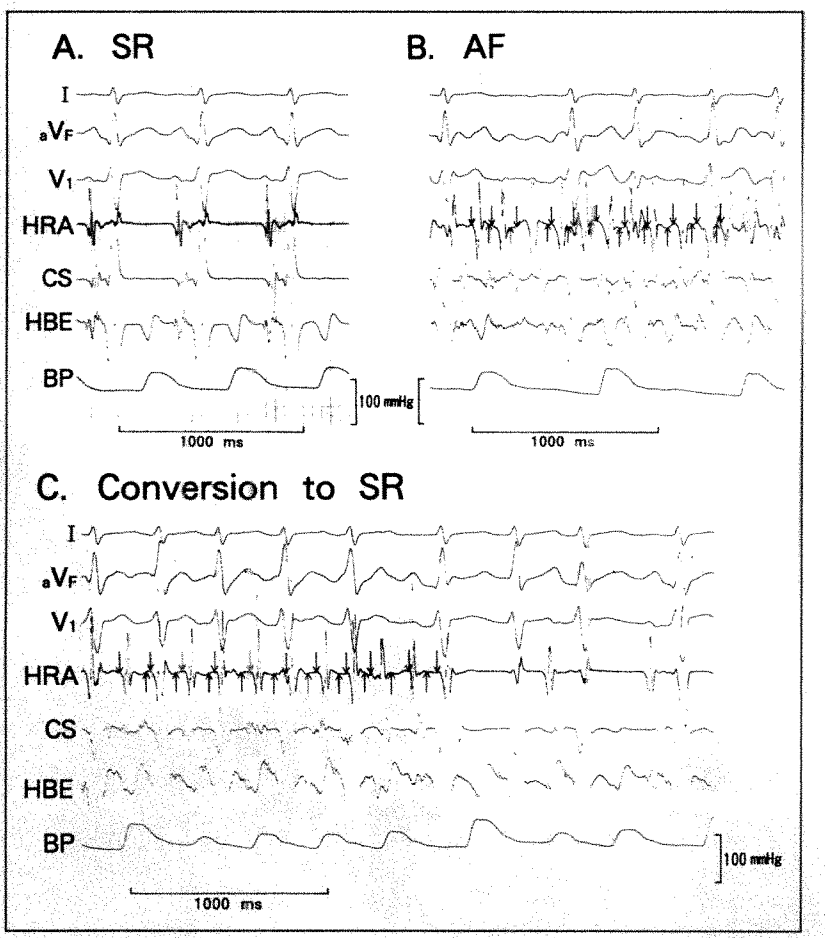


FIGURE 4. Electrophysiologic consequences in a group 2 patient with concealed Wolff-Parkinson-White syndrome to whom disopyramide was administered during atrial fibrillation (AF). *A.*, intracardiac electrograms during sinus rhythm (SR). The wavelength index was 1.16 during AF *(B.)*. After 30-minute continuation of AF, disopyramide was administered intravenously. Five minutes after infusion of the drug, AF terminated and the wavelength index increased to 1.24 just before conversion to sinus rhythm *(C.)*. BP = blood pressure; other abbreviations as in Figure 2.

trophysiologic properties. The size of intramyocardial reentrant circuits without a gross anatomic obstacle is determined by electrophysiologic properties and is compatible to the wavelength. With this background, circulating impulses of AF are considered to travel along the shortest possible route, resulting in a connection of tail and head of the impulse.[17] The wavelength of microreentrant circuits of AF cannot be measured directly by electrodes in an electrophysiologic study. However, we defined the wavelength index, a semiquantitative value, as the aforementioned expression. During AF, the wavelength indexes in group 1 were longer than those in group 2, which implies that AF is likely to terminate if the size of the microreentrant circuit is larger. Provided that the size of the reentrant circuit is larger, a greater amount of slow conduction is necessary to maintain the arrhythmia incorporating the circuits. In contrast, such arrhythmia is stabilized because the circuit size is small.

Wavelength indexes in all of the group 1 patients increased just before AF terminated spontaneously. This fact implies either that microreentrant circuits extend just before termination or that slow conduction is cancelled at the conversion to a sinus rhythm. When lengthening of wavelength occurs, slow conduction will relatively decrease and a collision of the impulse with another impulse is more probable. A prolongation of the wavelength may result in an incremental change in the average value in the circuit size. The total number of wandering impulses will decrease and the opportunity to promote fusion and disappearance of wavelets will increase because the tissue quantity in a definite atrium is constant. Our hypothesis on the relation between the wavelength index and the characteristics of a reentrant circuit is presented in Figure 5.

Dysopyramide is a useful drug for terminating AF and maintaining sinus rhythm in humans.[18-20] However, the underlying mechanism for termination of AF and maintenance of sinus rhythm caused by this drug is not clearly understood. For example, class Ia antiarrhythmic drugs of Vaughan Williams' classification will prolong refractoriness of the atrium, but these drugs may deteriorate slow conduction by decreasing conduction velocity to a certain degree. In 3 group 2 patients, wavelength indexes increased just before AF terminated as a result of the intravenous administration of disopyramide. The incremental change in wavelength indexes was mainly due to prolongation of the ff interval without significant changes in the f width. Prolongation of the refractory periods caused by disopyramide resulted in extension of the circuits, which was considered to be a major determinant for termination of AF. Thus, a condition required for the drug to terminate AF and to maintain sinus rhythm is to prolong refractory periods without enhancing slow conduction. However, currently available drugs cannot satisfy this condition absolutely. It is important to develop medications that prolong refractory periods without decreasing conduction velocity resulting in the incremental alteration in the wavelength.

Study limitation: It is impossible to measure the wavelength of the impulse during AF directly, and our wavelength index is a semiquantitative value reflecting the size of microreentrant circuits. Wavelength indexes were measured solely in the high right atrium because atrial deflections were difficult to identify because of superimposing ventricular electrograms in other portions of the atria. We do not believe that the high right atrium is the sole portion involved in the maintenance of AF. Thus, further studies on the other parts of the atrium are necessary.

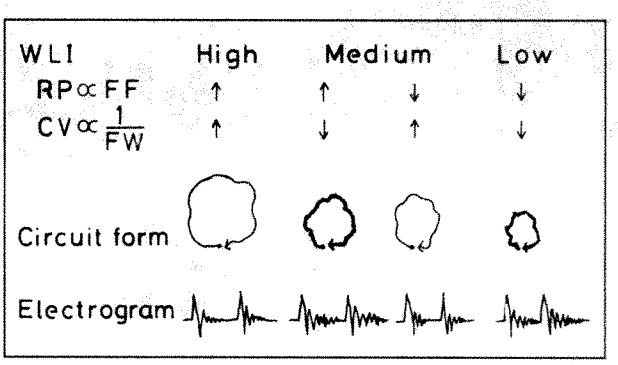


FIGURE 5. Relation between wavelength and reentrant loop. The wavelength is the product of refractory period (RP) and conduction velocity (CV). Refractory periods are correlated with the mean ff interval (FF) and the conduction velocity is correlated inversely with the mean f width (FW). Thus, the wavelength index (WLI) was defined as: WLI = FF/FW. Electrogram = intraatrial potentials, the configurations of which are considered to be related to the characteristics of reentrant circuits. See text for details.

An analysis of wavelength is not sufficient as an explanation of the origin of AF; vulnerability of atrial muscle and abnormal cellular electrophysiologic properties are important factors for elucidating the origin of AF.[21,22] In contrast, abnormal electrophysiology, which shortens refractory periods and decreases conduction velocity, will make the wavelength shorter. Thus, atrial vulnerability based on abnormal cellular electrophysiology may in part reflect a shorter wavelength from the perspective of the macroscopic mechanism. Furthermore, anisotropy in electrical properties in the atria is also considered to be involved in the origin and perpetuation of AF. Structural complexities produced by the inhomogeneous distribution of the connections between cells and between muscle bundles are important in the propagation of depolarization in cardiac muscle.[23,24]

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Most commonly occurring side effects comparable to placebo

Adverse Effect	ZOCOR® (Simvastatin) (n=1,583)	Placebo (n=157)
Headache	**3.5%**	5.1%
Abdominal pain	**3.2**	3.2
Constipation	**2.3**	1.3
Upper respiratory infection	**2.1**	1.9
Diarrhea	**1.9**	2.5
Flatulence	**1.9**	1.3
Asthenia	**1.6**	2.5
Nausea	**1.3**	1.9
Dyspepsia	**1.1**	–

Adverse experiences occurring at an incidence ≥ 1% in patients treated with ZOCOR in controlled clinical trials, regardless of causality.

In controlled clinical trials and open extensions (n=2,423),
Only 1.4% of patients were discontinued due to a drug-related adverse event.

Liver dysfunction
It is recommended that liver function tests be performed during therapy with simvastatin. Serum transaminase levels, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks for the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals).

Skeletal muscle
Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected.

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

ONCE-A-DAY

ZOCOR®

(SIMVASTATIN)

ZOCOR is available in 5-mg, 10-mg, 20-mg, and 40-mg tablet strengths.

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of HMG-CoA reductase inhibitors such as ZOCOR® (Simvastatin) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If a patient becomes pregnant while taking this drug, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: ***Liver Dysfunction:*** **Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials.** When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed during therapy with simvastatin. Serum transaminase levels, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks for the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations persist beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms, and did not require interruption of treatment.

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients; or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had preexisting renal insufficiency, usually as a consequence of longstanding diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between myopathy and increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors, the daily dosage should not exceed 10 mg/day in patients who are taking cyclosporine (see DOSAGE AND ADMINISTRATION in Prescribing Information).

Simvastatin therapy should be temporarily withheld or discontinued in any patient who has an acute, serious condition suggestive of a myopathy or who has a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected.

PRECAUTIONS: ***General:*** Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND USAGE in Prescribing Information).

Simvastatin may cause elevation of CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia: ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle.*

Antipyrine: Because simvastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In healthy male volunteers, there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR® (Simvastatin) and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: Simvastatin therapy appeared to enhance slightly the anticoagulant effect of warfarin (mean changes in prothrombin time less than 2 seconds) in normal volunteers maintained in a state of low therapeutic anticoagulation. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies* in Prescribing Information). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients who are also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and in mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3 to 33 times higher in mice than in humans given 40 mg of ZOCOR.

In a separate 92-week carcinogenicity study in mice at doses of up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2 to 4 times higher than in humans given 40 mg simvastatin as measured by AUC.

In a 2-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC). Preliminary results from a second 2-year rat study indicate an increase in the incidence of thyroid and liver tumors in male and female rats at doses that produce exposure levels ≥29 times (based on AUC) those achieved in humans at a dosage of 40 mg/day. Liver tumors are found in rodents with all the chemically similar drugs of this class. No increased incidence of tumors was observed at doses that produce exposure levels 15 times (based on AUC) those seen in man.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation at 10 mg/kg/day (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy: *Pregnancy Category X.* See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses of up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Simvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If a woman becomes pregnant while taking simvastatin, it should be discontinued and the patient should be advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children or adolescents with simvastatin is not recommended at this time.

ADVERSE REACTIONS: In the controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR® (Simvastatin). Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences: Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N=1,583)	Placebo (N=157)	Cholestyramine (N=179)	Probucol (N=81)
Body as a Whole				
Abdominal pain	3.2%	3.2%	8.9%	2.5%
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	6.2

The following effects have been reported with drugs in this class:

Skeletal: Myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis; hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia; vomiting.

Skin: Alopecia.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CPK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE: Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses, the only signs seen in dogs were emesis and mucoid stools.

There have been no cases of clinically significant overdosage with ZOCOR in humans. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

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Long-Term Outcome of Paced and Nonpaced Patients with Severe Carotid Sinus Syndrome

Michele Brignole, MD, Carlo Menozzi, MD, Gino Lolli, MD, Nicola Bottoni, MD, and Germano Gaggioli, MD

The natural history of patients with severe carotid sinus syndrome, and the efficacy of permanent pacemaker treatment are not clearly known. A randomized treatment/nontreatment prospective study was performed in 60 patients affected by carotid sinus syndrome whose symptoms were judged to involve risk of major trauma or interfered with their daily activity. They were randomly assigned to 2 groups: 28 patients to no therapy (nonpacing group), and 32 to VVI (n = 18) or DDD (n = 14) pacemaker implant (pacing group).

Syncope recurred in 16 patients (57%) of the nopacing group (mean follow-up 36 ± 10 months) and in only 3 (9%) of the pacing group (mean follow-up 34 ± 10 months) (p = 0.0002); moreover, 19 (68%) in the nonpacing group needed a secondary pacemaker implant because of the severity of symptoms. The actuarial rate of absence of syncopal recurrence after 1, 2, 3 and 4 years was 64, 54, 38 and 38%, respectively, for the nonpacing group, and 100, 97, 93 and 84%, respectively, for the pacing group (p = 0.0001). The actuarial rate of absence of minor symptoms after 1, 2, 3 and 4 years was 21, 14, 7 and 7%, respectively, for the nonpacing group and 66, 43, 27 and 27%, respectively, for the pacing group (p = 0.002). Reproducibility of carotid sinus reflex was tested after 15 ± 8 months in 54 patients; an abnormal response to carotid sinus massage persisted in all 54.

In conclusion, symptoms recur in most patients with untreated carotid sinus syndrome, and pacing is a useful therapy for preventing recurrences.

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Generally, carotid sinus syndrome is considered a relatively benign condition with a high probability of spontaneous remission of symptoms, and a mortality that is unaffected by therapy. Two recent, large, uncontrolled studies of pacing therapy in patients affected by severe carotid sinus syndrome revealed that during long-term follow-up, syncope recurred in 9 to 13% of patients with cardioinhibitory or mixed types of sinus syndrome.[1,2] Uncontrolled studies of untreated or medically-treated patients (probably affected by less severe disease) showed that syncope recurred in only approximately a quarter of cases.[3–6]

Therefore, questions arise concerning what is the real usefulness of pacing therapy and which patients need this therapy.[4] In fact, the natural history of patients with recurrent severe symptoms is not well known, because these patients are usually treated. A randomized, prospective study comparing homogeneous paced and nonpaced patients could provide answers to these questions; in this article, we report the long-term follow-up results of such a study.

METHODS

Selection of patients: A group of 60 patients with severe carotid sinus syndrome was recruited from November 1986 to May 1989 from the emergency room, inpatient service or ambulatory program. Preliminary short-term results of the first 35 patients enrolled were previously presented.[7]

To be included in the study, patients had to fulfil the following criteria: 1. history of recurrent episodes of syncope or presyncope that: had caused major trauma, or was judged to involve risk of future trauma or death because of sudden onset and the activity of the patient; or (because of frequency and intensity) caused the patient discomfort and interfered with daily activity.

2. Reproduction of spontaneous symptoms by means of carotid sinus massage that caused a ventricular asystole lasting ≥3 seconds. The response to the massage (in absence of cardioactive and vasoactive drugs) had to be reproducible within a few days. Digital massage of the carotid sinuses was performed sequentially on the right and left sides for 10 seconds, in the supine and erect positions. Surface electrocardiogram and cuff blood pressure were monitored continuously. The massage was repeated after suppression of the cardioinhibitory reflex by intravenous atropine infusion (0.02 mg/kg) to assess the contribution of the vasodepressor component (which may otherwise be hidden). Carotid sinus syndrome was defined as cardioinhibitory type when the reduction in systolic blood pressure after atropine administration was <50 mm Hg, and as mixed type when

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TABLE I Features of Nonpaced and Paced Groups Before Randomization

	Nonpaced Group (n = 28)	Paced Group (n = 32)
Age (yr ± 1 SD)	70.1 ± 10.7	69.4 ± 9.7
Male sex (%)	21 (75%)	27 (84%)
Symptoms		
Syncope	27 (96%)	31 (97%)
Mean episodes/pt.	3.1 ± 2.2	3.4 ± 5.2
Mean episodes/pt. in previous 12 months	2.1 ± 2.0	1.8 ± 1.1
Severe dizziness	20 (71%)	20 (62%)
Mild dizziness	21 (75%)	23 (72%)
Major trauma (fractures)	3 (11%)	3 (9%)
Carotid sinus hypersensitivity		
Cardioinhibitory type	13 (46%)	14 (44%)
Mixed type	15 (54%)	18 (56%)
Mean ventricular asystole (sec)	7.1 ± 2.0	7.8 ± 2.2
Associated cardiac diseases		
Overall	18 (64%)	22 (69%)
Atherosclerotic	6	12
Hypertensive	9	8
Dilated	1	0
Myocardial infarction	2	2
Radiologic/echocardiographic cardiac enlargement	15 (54%)	16 (50%)
Bundle branch block	6 (21%)	6 (19%)
1° AV block	4 (14%)	1 (3%)
Mild sinus bradycardia	12 (43%)	12 (38%)

AV = atrioventricular.

the decrease was ≥50 mm Hg. This method was widely described and validated in previous published reports.[2]

3. No other identifiable cause of symptoms despite a careful history, full physical examination, baseline laboratory testing, neurologic evaluation, 12-lead electrocardiogram, prolonged electrocardiographic monitoring (either ambulatory or telemetry) of ≥24 hours' duration in a coronary care unit, chest x-ray, echocardiographic evaluation, intracavitary electrophysiologic study, and definite evaluation of any clinical or historical finding suggestive of another cause of the symptoms.

Because carotid sinus syndrome frequently coincides with sinus or atrioventricular node dysfunction,[3,8,9] we included patients with mild signs of sinus dysfunction or atrioventricular conduction abnormalities that were judged clinically insufficient to cause symptoms. Furthermore, we excluded patients with: persistent diurnal sinus bradycardia <50 beats/min; intermittent or mild sinus bradycardia <60 beats/min with abnormal electrophysiologic evaluation of sinus node function (abnormal intrinsic heart rate <2 SD of age-related predicted normal value,[10] or sinus node recovery time >2 seconds); 2- or 3-degree atrioventricular block; baseline HV interval ≥70 ms; or infrahisian 2- or 3-degree atrioventricular block during incremental atrial pacing or intravenous ajmaline administration (1 mg/kg). The listed electrocardiographic abnormalities were present in 18 patients who were therefore excluded.

Initially, 79 patients were identified. Of these, 19 patients were excluded because of: extremely severe symptoms that needed an immediate pacemaker implant (6 cases); or difficulty in obtaining reliable data during follow-up because of advanced age, mental state or remote place of residence of the patient, or refusal to participate in the study, or a combination (13). The remaining 60 patients underwent randomization. Their clinical characteristics are listed in Table I.

Study protocol: A randomized treatment/nontreatment prospective comparative study was undertaken. The randomizing sequence was obtained from a table of random numbers. Patients assigned to the pacing group (n = 32) promptly received a permanent VVI (n = 18) or DDD (n = 14) pacemaker. The VVI mode was preferred for the cardioinhibitory type of carotid sinus syndrome without symptomatic VVI pacemaker effect (in standing position) and for the mixed type without symptomatic pacemaker effect, ventriculoatrial conduction or orthostatic hypotension; the DDD mode was reserved for the other cases. The decision was obtained on the basis of previous studies[2,11] showing that when a proper preimplant stratification of VVI failure risk is performed, the subsequent outcome of VVI-paced patients is as favorable as that of DDD-paced ones. The nonpaced patients received neither pacemaker nor any other therapy. All patients were advised against use of medications that potentially influence the carotid sinus reflex (i.e., β blockers, digitalis, antiarrhythmic drugs, and so forth).

During follow-up patients were trained to record their symptoms daily in a diary according to the following definitions (modified from Morley et al)[12]: mild dizziness: dizziness, sudden weakness, lightheadedness, near fainting, blurring of vision, confusion not requiring change of posture, and insufficient to interfere with activity; severe dizziness: same as mild dizziness, but requiring patients to change posture or preventing activity; and syncope: sudden unexplained loss of consciousness. Patients were also examined in our departments after 1, 2 and 4 months, and then every 6 months.

Statistical analysis: Student's t test for unpaired data was used for quantitative comparisons; the Fisher exact test was used for comparison between proportions; the symptom recurrence rate of the study cohorts was estimated with the Kaplan-Meier actuarial life-table method and compared with p value based on the log-rank test.[13,14]

RESULTS

Natural history of carotid sinus syndrome: The rates of recurrence of syncope and minor symptoms in the nonpacing group during the 36 ± 10 months of follow-up are summarized in Table II, and Figures 1 and 2; at 1, 2, 3 and 4 years, the actuarial rates of absence of syncope were 64, 54, 38 and 38%, respectively, and those of absence of any symptoms were 21, 14, 7 and 7%, respectively. When follow-up was subdivided into

consecutive 6-month periods (4 months for the first period), symptoms occurred in a minority of total periods (Table II). Actuarial rates for absence of syncope were similar in the cardioinhibitory and mixed forms (Figure 3).

Nineteen patients (68%) needed secondary pacemaker implant, because of recurrence of severe symptoms. No patient had major syncope-related trauma during follow-up.

Comparison between paced and nonpaced patients: Clinical and laboratory investigation revealed that the 2 groups resulting from randomization were sufficiently homogeneous (Table I).

During the 34 ± 10 months of follow-up, the pacing group was characterized by a significantly lower rate of recurrence of symptoms (Table II, and Figures 1 and 2). Indeed, actuarial rates after 1, 2, 3 and 4 years revealed absence of syncope in 100, 97, 93 and 84% of patients, respectively, and absence of any symptoms in 66, 43, 27 and 27% of patients, respectively. Syncope recurred in 1 patient with a VVI pacemaker and in 2 with a DDD pacemaker. Statistically significant differences in rates of syncopal recurrence between the 2 groups also persisted when patients were subdivided into cardioinhibitory and mixed subgroups of carotid sinus syndrome (Figure 3).

Withdrawal from nonpacing group: After 8.2 ± 10 months, 19 patients withdrew from follow-up, because they needed a pacemaker implant (VVI in 12 cases, DDD in 7). The reasons for implant were recurrence of syncope, alone or in association with minor symptoms (n = 15), or frequent recurrence of distressing severe or mild dizziness (n = 4). The decision to implant was obtained by us in cases with syncopal recurrences and was requested by the patient or physician in other cases. Pacing mode was determined according to the aforementioned criteria (see Methods).

An intrapatient comparison was performed between the periods before and after secondary pacemaker im-

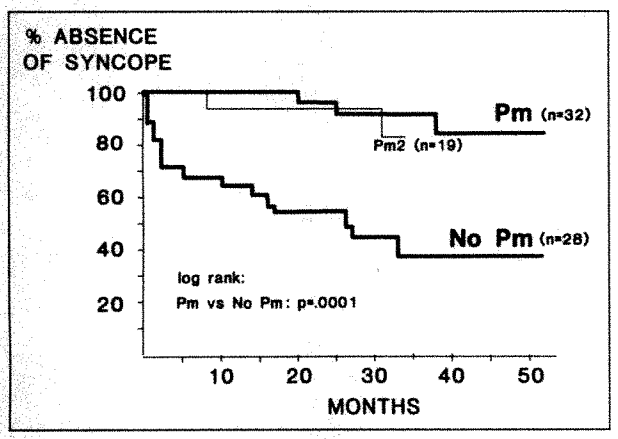


FIGURE 1. Actuarial rates of recurrence of syncope (Kaplan-Meier estimate) in groups of patients randomized to pacemaker implant (Pm) or no therapy (No Pm). Actuarial rate of subgroup of originally nonpaced patients who later received secondary pacemaker implant (Pm2) is superimposed.

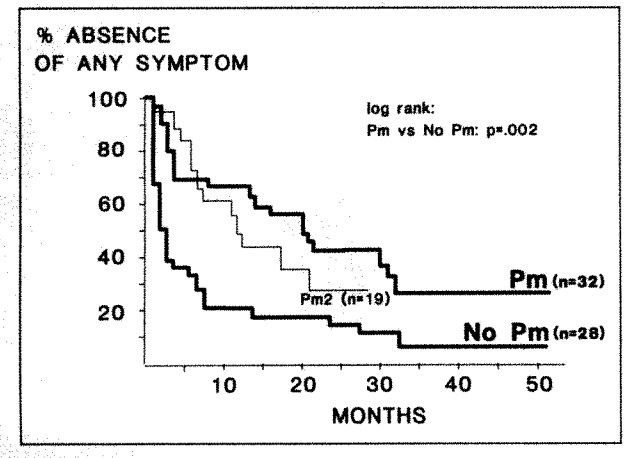


FIGURE 2. Actuarial rates of recurrence of syncope or minor symptoms (Kaplan-Meier estimate) in groups of patients randomized to pacemaker implant (Pm) or no therapy (No Pm). Actuarial rate of subgroup of initially nonpaced patients who later received a secondary pacemaker implant (Pm2) is superimposed.

TABLE II Follow-Up Results in Paced and Nonpaced Groups

	Nonpaced Group	Paced Group	p Value
Syncope			
Total pts.	16 (57%)	3 (9%)	0.0002
Total episodes	22	4	
Symptomatic/asymptomatic follow-up*	16/112 (14%)	3/219 (1%)	
Severe dizziness			
Total pts.	9 (32%)	8 (25%)	0.37
Symptomatic/asymptomatic follow-up*	11/112 (10%)	10/219 (5%)	
Mild dizziness			
Total pts.	18 (64%)	22 (69%)	0.46
Symptomatic/asymptomatic follow-up*	34/112 (30%)	40/219 (18%)	
Secondary pacemaker implant	19 (68%)	—	

*For each patient, follow-up was subdivided into consecutive 6-month periods (4 months for first period after randomization); numbers represent sum of symptomatic or asymptomatic periods of all patients.

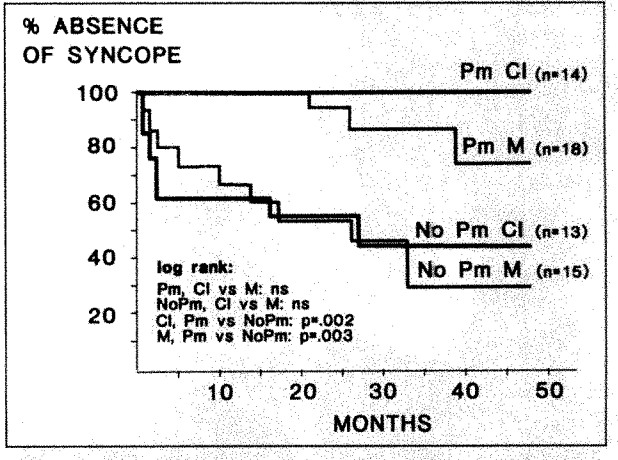


FIGURE 3. Actuarial rates of recurrence of syncope (Kaplan-Meyer estimate) in patients with cardioinhibitory (CI) and mixed (M) types of carotid sinus syndrome in paced (Pm) and nonpaced (No Pm) groups. ns = not significant.

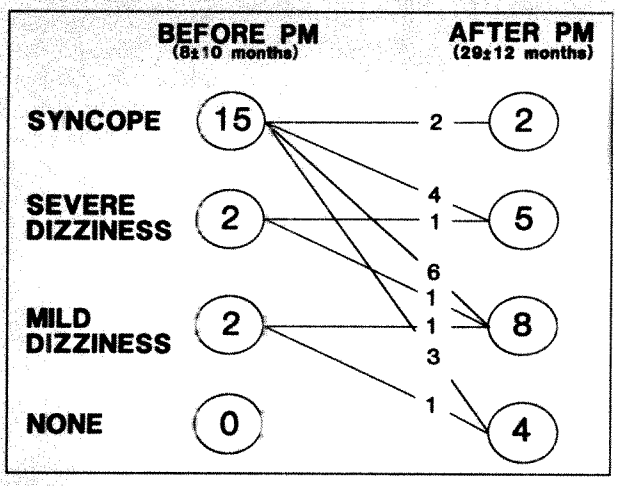


FIGURE 4. Follow-up in 19 patients originally randomized to no therapy who later received pacemaker (PM) because of persistence of symptoms. *Left*, symptoms occurring from randomization to secondary pacemaker implant; *right*, symptoms occurring after pacemaker implant.

plant (Figure 4). The actuarial rates of absence of syncope and any symptoms after the secondary pacemaker implant were similar to those observed in the pacing group (Figures 2 and 3). At 1, 2 and 3 years, the predicted rates of absence of syncope were 94, 94 and 84%, respectively, and those of absence of any symptoms were 49, 28 and 20%, respectively.

Reproducibility of the carotid sinus reflex: Carotid sinus massage was repeated in 54 patients after 15 ± 8 months (range 2 to 30) to study the long-term development of the carotid sinus reflex. In paced patients, the massage was performed during the temporary inhibition of the stimulus output of the implanted generator. The test remained positive in all 54 patients (100% reproducibility), with both >3-second asystole and reproduction of symptoms. Mean asystole was 7.7 ± 2.1 seconds (range 3 to 13) during the initial carotid sinus massage, and 6.5 ± 1.6 seconds (range 3 to 10) during the second massage. Of 49 patients who had syncope induced during the first test, 46 had syncope again during the second one (3 only dizziness); of 5 patients who had dizziness during the first test, 4 had dizziness again during the second one (1 syncope).

Major clinical events: During follow-up we observed 9 deaths, resulting in a 5-year actuarial predicted survival of 67%; 4 deaths occurred in the pacing group (3 cardiovascular nonsudden and 1 noncardiovascular), and 5 occurred in the nonpacing group (2 cardiovascular nonsudden, 1 sudden and 2 noncardiovascular).

The following nonfatal clinical events occurred in the pacing and nonpacing groups: stroke (5 vs 5), myocardial infarction (1 vs 4), atrial fibrillation (4 vs 6) and asymptomatic ventricular tachycardia (0 vs 1). No other cause for syncope was found in any patient during follow-up.

DISCUSSION

Natural history of carotid sinus syndrome: This study found that the natural history of the severe carotid sinus syndrome (for which at present the indication for pacemaker therapy is often considered) is characterized by a high rate of symptom recurrence (Table II, and Figures 1 and 2); although many patients have early recurrences, others remain free of symptoms for a long time. A pacemaker implant is frequently necessary because of recurrences.

Therefore, the natural history of severe carotid sinus syndrome appears to be worse than that of less severe forms described in the literature, which are not usually paced. Sugrue et al[4] observed recurrence of syncope in 3 of 13 nontreated patients (23%) and in 4 of 20 medically treated ones (20%) affected by syncope or presyncope during a median 39-month follow-up. Huang et al[3] observed recurrence of syncope in 1 of 8 untreated patients (12%) during 42 ± 19 months of follow-up. A 27% recurrence rate of syncope was observed by Brignole et al[6] in 242 patients affected by cardioinhibitory and vasodepressor types of carotid sinus syndrome during 44 ± 24 months of follow-up. The fact that natural history is determined by clinical presentation was also confirmed by the study of Blanc et al[5] who, during 29 ± 16 months of follow-up, observed recurrence of syncope in 9 of 18 patients (50%) with history of syncope and in 1 of 15 (7%) with history of dizziness, or no symptoms. A similar outcome was observed by Walter et al.[15]

Whereas recurrence of symptoms is unpredictable, reproducibility of the abnormal reflex to carotid sinus massage is excellent. Such reproducibility has been questioned by other investigators[15] who noted a fluctuation in carotid sinus sensitivity, with normal responses during symptom-free periods. An explanation for our good reproducibility is that our patients had severe asystolic reflexes and that we used a standardized stimulation protocol.

Effects of cardiac pacing: Because of its randomized design, the results of this study are unequivocal and demonstrate the use of pacing therapy in patients with the cardioinhibitory and mixed forms of carotid sinus syndrome (Table II, and Figures 1 and 2). The favorable effect of cardiac pacing was also proved in patients of the nonpacing group who received the secondary pacemaker implant, because of recurrence of severe symptoms (Figures 1, 2 and 4). Indeed, after the implant, the actuarial curve of absence of symptoms in this subgroup was comparable to that of the pacing group.

However, during long-term follow-up syncope can occasionally recur (as well as minor symptoms), even if the frequency of recurrence, and the ratio between symptomatic and asymptomatic periods dramatically decrease in comparison with those of untreated patients. Other long-term studies showed similar percentages of recurrence of symptoms despite pacing therapy[1,2]; recurrences have been underestimated in studies with short-term follow-up.[11,15,16]

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Usefulness of Clinical Characteristics in Predicting the Outcome of Electrophysiologic Studies in Unexplained Syncope

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Guidelines for the use of electrophysiologic studies in syncope have not yet been formulated. To confirm the sensitivity and specificity of a previously derived model to predict the results of electrophysiologic testing in syncope, the importance of 6 clinical predictors was assessed in a new data set of 141 consecutive patients with unexplained syncope who were referred for electrophysiologic studies. The 6 predictors were: organic heart disease; premature ventricular beats, sinus bradycardia, first-degree heart block and bundle branch block by electrocardiogram; and nonsustained ventricular tachycardia by Holter monitor. Organic heart disease and nonsustained ventricular tachycardia by Holter monitoring were highly sensitive for serious ventricular tachyarrhythmias at electrophysiologic study (sensitivity 100%), whereas sinus bradycardia, first-degree heart block or bundle branch block by electrocardiogram were sensitive for bradyarrhythmic outcomes (sensitivity 79%). Because these variables are so sensitive for serious outcomes of electrophysiologic testing in syncope, invasive studies in patients without these clinical predictors are likely to be of very low diagnostic yield.

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Syncope, a transient loss of consciousness with loss of postural tone, is a prevalent,[1] disabling,[2] expensive[3] and dangerous clinical disorder that is often difficult to diagnose.[4–6] Electrophysiologic testing has evolved as a useful diagnostic tool in syncope,[7–9] with a large proportion of syncope patients in several series demonstrating severe conduction abnormalities or serious tachyarrhythmias during electrophysiologic testing.[10–15] However, guidelines for the use of electrophysiologic testing in syncope have not been developed, and whereas 2 studies proposed predictive models for this purpose,[16,17] neither model has undergone systematic validation.

In a recent study, Linzer et al[18] developed a model for predicting the outcome of electrophysiologic testing in syncope by using logistic regression in a data base of 179 patients. Six clinical predictors were found. Three variables predicted ventricular tachyarrhythmias (organic heart disease, frequent premature ventricular contractions by electrocardiogram, and nonsustained ventricular tachycardia by Holter monitoring) and 3 predicted bradyarrhythmic outcomes (sinus bradycardia, first-degree heart block and bundle branch block by electrocardiogram). These variables had excellent sensitivity (87%) for detecting patients with positive electrophysiologic studies, although the specificity was predictably lower (55%). The model was preliminarily validated on a separate data set of 135 patients generated from the clinical literature. Of note, the ability of the model to detect patients with life-threatening ventricular arrhythmias at electrophysiologic study ranged from 88% in the validation sample to 100% in the training (original) data set.

The purposes of this study were twofold: (1) to further validate the predictive model in a different clinical setting and (2) to use different combinations of clinical predictors to attempt to improve the specificity of the model without diminishing the sensitivity.

METHODS

Patient selection and evaluation: The study group comprised 141 consecutive patients who underwent electrophysiologic evaluation for syncope from January 1983 to January 1990. The initial noninvasive evaluation of each patient consisted of a thorough history, physical examination and 12-lead electrocardiogram. Orthostatic blood pressure determination and carotid sinus massage were performed in all patients. Most patients also underwent ≥24 hours of Holter monitoring, and determination of left ventricular function with either echocardiographic or radionuclide ventriculographic studies, or cardiac catheterization.

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After informed consent was obtained, electrophysiologic studies were performed in the fasting, unsedated state. Drugs with antiarrhythmic effects were discontinued for ≥5 drug half-lives before the study. Three or four electrode catheters were introduced through the femoral veins and positioned in the high right atrium and right ventricle, and across the tricuspid valve to record the His bundle electrogram. Surface electrocardiographic leads V_1, I and III, and intracardiac recordings were displayed simultaneously on an oscilloscope and recorded on FM tape for subsequent storage. Programmed electrical stimulation was performed using a custom Medtronic Stimulator delivering square-wave pulses at 2 times the diastolic threshold and 2 ms pulse-width duration.

Collection of clinical data: Specific historical data and physical findings were extracted from patient records. A 3-page standardized data format was used for data collection. The data were computer coded and cross-checked by the study technician. Strict diagnostic criteria were used for assessment of all clinical predictor variables.

(1) Historical aspects: The following historical variables were obtained: age, sex, duration and number of syncopal episodes, medications and other significant medical history.

(2) Presence and type of heart disease: Absence or presence and type of organic heart disease were determined on the basis of history, physical examination and electrocardiogram in all patients, echocardiography in 99 patients, radionuclide ventriculography in 10, and cardiac catheterization in 12.

(3) Electrocardiographic abnormalities: An electrocardiogram was obtained on admission in all patients, and information recorded included disturbances of rhythm or conduction or both, prior myocardial infarction and presence or absence of left ventricular hypertrophy. The following definitions were used to assess potential clinical predictors: "frequent premature ventricular contractions": ≥3 premature ventricular contractions/min, multiform or salvos of premature ventricular contraction complexes; first-degree heart block: PR interval ≥0.2 second; bundle branch block: QRS duration ≥0.12 second with either a left or right bundle branch block pattern, or intraventricular delay; and sinus bradycardia: ≤50 beats/min.

(4) Ambulatory electrocardiographic monitoring: One hundred twenty-three patients underwent 24 hours of Holter monitoring. Nonsustained ventricular tachycardia was defined as ≥3 consecutive ventricular premature depolarizations, terminating spontaneously before 30 seconds.

Clinical variables evaluated: The existence of organic heart disease, frequent premature ventricular contractions on electrocardiogram, and nonsustained ventricular tachycardia on Holter monitoring were tested for predicting tachyarrhythmias at electrophysiologic study, whereas sinus bradycardia, first-degree heart block and bundle branch block on surface electrocardiogram were tested for their ability to detect bradyarrhythmias at electrophysiologic study. Of the electrocardiographic and electrophysiologic parameters measured, the following variables were analyzed to determine the outcomes on electrophysiologic studies: spontaneous intervals (AH and HV), corrected sinus node recovery times after overdrive suppression of the sinus node at 3 drive cycle lengths (600, 500 and 400 ms), shortest atrial pacing cycle length with 1:1 atrioventricular conduction, and atrioventricular nodal effective refractory period by the extrastimulus technique. The ventricular protocol consisted of single and double extrastimuli during the patient's routine rhythm, and 3 drive cycle lengths (600, 500 and 400 ms) in the right ventricular apex. If a sustained ventricular arrhythmia was not induced with single or double extrastimuli, triple extrastimuli were delivered during the patient's natural rhythm.[19]

TABLE I Clinical Characteristics of 141 Patients with Syncope of Unknown Origin Undergoing Electrophysiologic Testing

Age (yr)	59 ± 17
Sex: men/women	96 (68%)/45 (32%)
Recurrent syncope	91 (64%)
Receiving antiarrhythmic medications at time of syncope	53 (38%)
Organic heart disease:	
None	44 (31%)
Coronary artery disease	76 (54%)
Cardiomyopathy (nonhypertrophic)	15 (11%)
Hypertrophic cardiomyopathy	4 (3%)
Preexcitation syndromes	2 (1%)
Other*	27 (19%)

*Valvular and congenital heart diseases.

Outcomes of electrophysiologic studies: Results of electrophysiologic studies were assessed using strict diagnostic criteria. A ventricular tachyarrhythmic outcome was defined as either: (1) sustained ventricular tachycardia lasting ≥30 seconds, or needing overdrive pacing or direct-current countershock because of hemodynamic compromise, (2) reproducible nonsustained ventricular tachycardia of ≥6 beats with severe symptoms or hemodynamic compromise,[19] or (3) ventricular fibrillation induced by ≤2 ventricular extrastimuli. A bradyarrhythmic outcome was defined as either: (1) atrioventricular nodal effective refractory period ≥425 ms, (2) prolonged HV interval ≥90 ms, (3) prolonged corrected sinus node recovery time ≥1,000 ms, or (4) spontaneous infra-Hisian block or Mobitz II second-degree atrioventricular block during incremental atrial pacing. A supraventricular tachyarrhythmic outcome included patients with symptomatic supraventricular arrhythmias. "Borderline" arrhythmias not considered to be the cause of syncope were defined as nonsustained ventricular tachycardia (asymptomatic or <6 beats), asymptomatic supraventricular tachycardia and mildly prolonged corrected sinus node recovery times or HV intervals. A negative electrophysiologic study was defined as a study that did not demonstrate any of the aforementioned electrophysiologic abnormalities.

Statistical analysis: Based on either tachyarrhythmic or bradyarrhythmic outcomes, estimated odds ratios were calculated for each clinical predictor. Univariate analyses were performed first, followed by multivariate assessment using the Statistical Analysis System (Proc Logist). Sensitivity (true positives/[true positives

TABLE II Surface Electrocardiographic Findings in 141 Patients with Unexplained Syncope Undergoing Electrophysiologic Testing

Rhythm*	
Normal sinus	119 (84%)
Sinus bradycardia ≤50 beats/min	7 (5%)
Paced rhythm	4 (3%)
Artrial fibrillation	2 (1%)
Sinus tachycardia	1 (1%)
Frequent premature ventricular contractions	17 (12%)
Conduction disturbances	
Normal	69 (49%)
1° heart block	31 (22%)
Bundle branch block	41 (29%)
Left bundle branch block	14
Right bundle branch block	20
Interventricular delay	7

*More than 1 abnormality could be present on each electrocardiogram; thus total is >100%.

TABLE III Electrophysiologic Findings of 141 Patients with Syncope of Unknown Origin Undergoing Electrophysiologic Testing

Normal or boderline arrhythmias	97 (69%)
Ventricular tachyarrhythmias*	18 (13%)
Sustained ventricular tachycardia	11
Reproducible NSVT with symptoms	4
VF induced by ≤2 extrastimuli	7
Bradyarrhythmias	28 (20%)
Sinus node disease	0
AV nodal disease	12
His-Purkinje disease	16
Supraventricular tachyarrhythmias	4 (3%)

*Patients could have >1 outcome, thus total is >100%.
AV = atrioventricular; NSVT = nonsustained ventricular tachycardia; VF = ventricular fibrillation.

+ false negatives]) and specificity (true negatives/[true negatives + false positives]) were also calculated for individual and subgrouped clinical predictors.

RESULTS

Clinical characteristics: Clinical characteristics of the 141 patients (96 men and 45 women, mean age 59.1 years) in this study are listed in Table I. Organic heart disease was present in 69% of patients, with most (54%) having some form of coronary artery disease.

Noninvasive test results: The initial surface electrocardiographic findings are listed in Table II. Ambulatory electrocardiographic recordings were available in 87% of patients and revealed 31 patients to have nonsustained ventricular tachycardias. Left ventricular ejection fraction averaged 52%, with 25 patients (21%) having an ejection fraction <40%.

Results of the electrophysiologic studies (Table III): Electrophysiologic testing revealed 12% of patients (n = 18) to have ventricular tachyarrhythmic outcomes, and 20% (n = 28) to have bradyarrhythmic outcomes. Four patients had a symptomatic supraventricular tachycardia. Two of these patients had electrocardiographic evidence of preexcitation, 1 had a prior myocardial infarction, and the other had mitral valve prolapse with numerous runs of supraventricular tachycardia on Holter monitoring.

Validation of the model: The previously identified clinical predictors were for the most part highly correlated with outcome in this new data set (Table IV). Ventricular tachyarrhythmic outcomes were associated with organic heart disease and nonsustained ventricular tachycardia on Holter monitoring. Frequent premature ventricular contractions by electrocardiogram did not reach statistical significance as a predictor of ventricular tachycardia induction. Sinus bradycardia, first-degree heart block and bundle branch block predicted bradyarrhythmic outcomes at electrophysiologic study. All 18 patients with a ventricular tachyarrhythmic outcome had ≥1 tachyarrhythmia predictor (100% sensitivity). Of the 28 patients with bradyarrhythmic outcomes at electrophysiologic study, 22 had ≥1 bradyarrhythmic predictor (79% sensitivity). Use of the clinical predictors resulted in an overall sensitivity and specificity for any tachyarrhythmic or bradyarrhythmic outcome of 95 and 23%, respectively. Table V shows that as the number of clinical predictors increases, the proportion of patients with a positive electrophysiologic study tends to increase as well. These results do not change appreciably when patients with no objective cardiac evaluation (e.g., echocardiography) and no Holter monitoring are omitted from the calculations.

Modification of the model: An attempt was made to improve the model's specificity in predicting tachyarrhythmic outcomes. In this analysis (Table VI), individual components of the organic heart disease variable

TABLE IV Clinical Predictor Variables and Outcome of Electrophysiologic Testing: Results of Univariate and Multivariate Analyses

	Outcome		Univariate		Multivariate	
	Pos.	Neg.	OR (95% CI)	p Value	OR (95% CI)	p Value
Tachyarrhythmia predictors						
OHD	17	80	9.1 (1.2, 71.0)	0.01	8.0 (1.0, 63.1)	0.05*
PVCs	4	13	2.4 (0.7, 8.5)	0.16	1.4 (0.4, 5.6)	NS
NSVT	8	24	3.3 (1.2, 9.3)	0.02	2.8 (1.0, 8.0)	0.057*
Bradyarrhythmia predictors						
Sinus bradycardia	4	3	6.1 (1.3, 29.1)	0.01	11.4 (2.1, 61.8)	0.005
1° heart block	14	17	5.6 (2.3, 13.9)	0.001	5.5 (2.1, 14.5)	0.001
Bundle branch block	14	27	3.2 (1.4, 7.5)	0.006	2.9 (1.1, 7.5)	0.03

*Estimated from logistic regression including OHD and NSVT only.
PVCs were not significant when a 3-variable model was fit.
CI = confidence intervals; Neg. = negative; NS = not significant; NSVT = nonsustained ventricular tachycardia; OHD = organic heart disease; OR = odds ratio; Pos. = positive; PVCs = premature ventricular contractions.

(such as coronary artery disease with and without a history of myocardial infarction, or cardiomyopathy) were used to predict ventricular tachycardia. Additionally, a low ejection fraction (<40%) was assessed as a sole predictor of ventricular tachycardia. Improvements in specificity could not be realized without substantial losses in sensitivity (Table VI).

Predictive accuracy of key predictors: the importance of nonsustained ventricular tachycardia on Holter monitoring (Table VII): Certain predictors were identified in prior studies as being highly predictive of ventricular tachycardia at electrophysiologic study. These included low left ventricular ejection fraction,[16] coronary artery disease with prior myocardial infarction,[17] and nonsustained ventricular tachycardia on Holter monitoring.[15,17] We examined clinically relevant combinations of these variables to predict a life-threatening outcome (i.e., ventricular tachycardia). The addition of nonsustained ventricular tachycardia on Holter monitoring in patients with a low ejection fraction and no coronary artery disease significantly increased the likelihood of finding ventricular tachycardia at electrophysiologic study (Table VII). Overall, patients with a low ejection fraction and nonsustained ventricular tachycardia on Holter monitoring had a very high likelihood (4 of 9 patients [44%]) of having ventricular tachycardia found at electrophysiologic study.

Long-term follow-up: Follow-up was obtained in 99% of patients (median duration 24 months, range 1 to

TABLE V Probabilities of Ventricular Tachycardia and Bradyarrhythmic Outcomes by Risk Factors in 141 Patients Undergoing Electrophysiologic Studies for Unexplained Syncope

OHD	PVCs by ECG	NSVT by Holter	Pts. with Predictors	Pts. with Positive Outcome	Proportion
Ventricular Tachyarrhythmic Outcomes					
0	0	0	38	0	0.00
+	0	0	65	9	0.14
0	+	0	0	0	0.00
0	0	+	3	1	0.33
+	+	0	6	1	0.17
+	0	+	18	4	0.22
0	+	+	3	0	0.00
+	+	+	8	3	0.38

SB	1° HB	BBB	Pts. with Predictors	Pts. with Positive Outcome	Proportion
Bradyarrhythmic Outcomes					
0	0	0	79	6	0.08
+	0	0	5	3	0.06
0	+	0	25	5	0.20
0	0	+	15	4	0.27
+	+	0	1	0	0.00
+	0	+	1	1	1.00
0	+	+	15	9	0.60
+	+	+	0	0	0.00

BBB = bundle branch block; ECG = electrocardiogram; SB = sinus bradycardia; 1° HB = first-degree heart block; other abbreviations as in Table IV.

TABLE VI Modifications of Clinical Predictor Variables of a Ventricular Tachyarrhythmic Outcome: Attempts to Improve Specificity Without Loss of Sensitivity

			Organic Heart Disease Subgroups								
OHD	Frequent PVCs by ECG	NSVT on Holter	CAD Without MI	CAD with MI	Cardio-myopathy	Existence of Any OHD Subgroup	EF ≤40%	Pts. with Predictors	Pts. with Positive Outcome	Sensitivity (95% CI)	Specificity (95% CI)
+	0	0	NA	NA	NA	NA	NA	97	17	0.94 (0.91, 0.98)	0.35 (0.27, 0.43)
0	+	0	NA	NA	NA	NA	NA	17	4	0.22 (0.15, 0.29)	0.89 (0.84, 0.95)
0	0	+	NA	NA	NA	NA	NA	32	8	0.44 (0.36, 0.53)	0.80 (0.74, 0.87)
NA	NA	0	+	0	0	NA	NA	42	4	0.22 (0.15, 0.29)	0.69 (0.61, 0.77)
NA	NA	NA	0	+	0	NA	NA	34	8	0.44 (0.36, 0.53)	0.79 (0.72, 0.86)
NA	NA	NA	0	0	+	NA	NA	14	4	0.22 (0.15, 0.29)	0.92 (0.87, 0.96)
NA	NA	NA	NA	NA	NA	+	NA	85	15	0.83 (0.77, 0.90)	0.35 (0.27, 0.43)
NA	NA	NA	NA	NA	NA	NA	+	29	6	0.33 (0.26, 0.41)	0.81 (0.74, 0.88)

CAD = coronary artery disease; EF = ejection fraction; MI = myocardial infarction; NA = not assessed; other abbreviations as in Tables IV and V.

TABLE VII Predictive Values of Different Combinations of Key Predictor Variables for Ventricular Tachycardia at Electrophysiologic Study in 141 Patients with Unexplained Syncope

EF <40%	NSVT on Holter	CAD with MI	PVCs by ECG	Pts. with Predictors	Pts. with Positive Outcome	Positive Predictive Value	95% CI
+	0	+	0	6	1	0.17	0.00, 0.46
+	+	+	+ or 0	5	2	0.40	0.00, 0.83
+	0	0	0	11	0	0*	
+	+	0	+ or 0	4	2	0.50*	0.01, 0.99
0	0	0	0	63	5	0.08	0.01, 0.15
0	+	0	+ or 0	15	2	0.13	0.00, 0.31
0	0	+	0	13	3	0.23	0.00, 0.46
0	+	+	+ or 0	8	2	0.25	0.00, 0.55

*Difference in positive predictive values significant ($p < 0.01$) for finding NSVT on Holter monitor in patients with EF <40% and no coronary artery disease versus those without nonsustained VT (line 3 vs 4). Other comparisons (lines 1 vs 2, 5 vs 6, and 7 vs 8) are not significant.
Abbreviations as in Tables IV to VI.

79). Ninety-one percent of the 44 electrophysiologic study "positive" patients and 44% of the "negative" ones were treated. In follow-up, only 3 patients died suddenly (1 was electrophysiologic study positive, and 2 were negative). Similar recurrence rates (18%) were seen in electrophysiologic study positive and negative patients. Recurrence occurred in 100% (4 of 4) of electrophysiologic study positive patients who were not treated, and in only 10% (4 of 40) of those treated. Thus, treatment of electrophysiologic study positive patients was associated with a low rate of recurrence of syncope and sudden cardiac death.

DISCUSSION

We showed that a combination of clinical, electrocardiographic and Holter monitor findings can predict the outcome of electrophysiologic testing in syncope. In particular, serious ventricular tachyarrhythmias are predicted by the presence of organic heart disease and nonsustained ventricular tachycardia on Holter monitoring, whereas severe conduction system disease at electrophysiologic testing is predicted by bradycardia or conduction system abnormalities on the surface electrocardiogram. In patients without these abnormalities, important results at electrophysiologic study were seen infrequently. Our follow-up data suggest that determining patients with syncope who need electrophysiologic studies is important, because treatment of electrophysiologic study positive patients was associated with acceptably low rates of recurrence and sudden death.

One of the strengths of our study is the extent to which the clinical predictors were validated. The predictors evaluated by the current study were developed on a previous data set, preliminarily validated on a data set of patients culled from the clinical literature, and finally retested in the current protocol. Whereas prospective validation in yet another setting would be a useful final step in the evaluation of the clinical predictors, the 2 validation steps described previously provide strong evidence that these clinical variables are of substantial clinical importance.

The clinical predictors evaluated in the current study show some predictable overlap with those determined in previous efforts by other investigators. Organic heart disease is understandably the most important substrate for the production of malignant ventricular arrhythmias. Thus, most prior studies identified organic heart disease as a key predictor in determining the outcome of electrophysiologic testing in syncope. A position paper by the American College of Physicians[20] stated that electrophysiologic testing was indicated in syncope, particularly in patients with recurrent symptoms and organic heart disease.

Bundle branch block on surface electrocardiogram was a strong predictor in the current study, as well as in previous efforts by other investigators.[21] Sinus bradycardia and first-degree heart block were also found to be predictors of bradyarrhythmic outcomes. Of note, a recent study by Fujimura et al[22] reported a limited sensitivity of electrophysiologic testing for determining bradyarrhythmias as a cause of syncope in patients with transient bradycardia. Thus, our results are of particular importance, because they suggest which patients at high risk for bradyarrhythmic syncope may benefit from electrophysiologic testing.

Despite the known clinical importance of such variables as low left ventricular ejection fraction and prior myocardial infarction in predicting the occurrence of ventricular tachyarrhythmias at electrophysiologic study,[16,17] we were unable to improve the specificity of our model by using these individual variables instead of the overall variable of organic heart disease. Any attempt to "narrow in" on these key variables led to significant reductions in the sensitivity of the model.

There are several limitations to our study. First, our data were retrospectively collected from a data set of patients referred for electrophysiologic testing. Second, the number of subjects with a positive electrophysiologic study was relatively low. Third, the outcome under study was the result of the test and not long-term patient outcome. Fourth, the model does not predict supraventricular tachycardia at electrophysiologic study. However, all 4 patients with a supraventricular tachycardic outcome would have been identified by the model as needing electrophysiologic study. Finally, the low specificity of the model is less than may be desired; however, the high sensitivity for important outcomes is essential, and we showed that the specificity cannot be improved without sacrificing sensitivity.

The implications of this study for the practicing clinician are as follows: For patients with unexplained syncope and organic heart disease, the risk of a serious arrhythmia as the cause of syncope is considerable, and electrophysiologic testing should be strongly considered. Patients with heart disease and ventricular ectopy on electrocardiogram and Holter monitoring are at even higher risk, and should almost certainly undergo electrophysiologic testing. Patients with sinus bradycardia, first-degree heart block or bundle branch block by electrocardiogram are at risk for a bradyarrhythmic cause of syncope. These "medium-risk" patients can also be evaluated by electrophysiologic study, or alternatively may be suitable (if symptoms are frequent) for noninvasive evaluation with long-term ambulatory loop electrocardiographic recording[23,24] to attempt to capture the cardiac rhythm at the moment of syncope. Patients with none of the clinical predictors are at almost no risk for a serious ventricular arrhythmia and at very slight risk of a bradyarrhythmia. In these patients, invasive testing should not be performed.

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Estimation of Mitral Valve Area from Regression Analysis of the Pressure Gradient in Mitral Stenosis

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Estimation of mitral valve area (MVA) in the cardiac catheterization laboratory is prone to pitfalls because of the time required for calculations and inaccuracies in the measurement of cardiac output. Because the rate of decrease in the mitral gradient directly correlates with the severity of mitral stenosis, an on-line estimate of MVA at the time of catheterization may be possible with regression analysis of digitized pressure recordings. A total of 61 comparisons of mitral gradient measurements and MVA were obtained in 37 patients at diagnostic catheterization and in 24 patients after balloon mitral valvotomy. Linear and nonlinear regression parameters yielded pressure half-time values and empiric constants similar to those used in Doppler echocardiography for estimation of MVA. The correlations derived from linear analysis were as good as those obtained from nonlinear analysis: from linear analysis, $MVA_{regression} = 0.79 \cdot MVA_{Gorlin} - 0.03$; $r^2 = 0.64$, $p = 0.0001$; and from double exponential analysis, $MVA_{regression} = 0.86 \cdot MVA_{Gorlin} - 0.07$; $r^2 = 0.74$; $p = 0.0001$. The correlations were not significantly affected by the presence of mild to moderate mitral regurgitation or whether they were obtained after balloon valvotomy. In summary, linear regression analysis yields accurate estimates of MVA despite the theoretical superiority of nonlinear methods. On-line digital analysis of mitral gradient tracings may thus be useful at the time of diagnostic cardiac catheterization or balloon mitral valvotomy to assess the severity of mitral stenosis and the response to interventions.

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The Gorlin formula, introduced 40 years ago,[1] endures as the hemodynamic method of choice to calculate mitral valve area (MVA) despite efforts to define a better formulation. Many studies have shown that MVA correlates with the pressure half-time ($T\frac{1}{2}$) — the time for the mitral gradient to decrease to one-half its initial value (reviewed by Thomas and Weyman[2]). Pressure $T\frac{1}{2}$ values are frequently estimated from mitral gradient data that are approximated to a linear function despite fundamental principles which suggest that the decay in the mitral gradient is a nonlinear process. An exponential decay is expected if viscous resistance predominates (i.e., the rate of decrease in the pressure gradient is directly proportional to the magnitude of the gradient), whereas a parabolic decay in the pressure gradient is predicted if convective resistance prevails (the decay in the gradient is proportional to the square of the gradient).[3-6] A parabolic decay in the pressure gradient implies a linear decay in mitral velocity from the Bernoulli relationship, thus supporting the Doppler echocardiographic assessment of mitral stenosis,[7] if left atrial and left ventricular compliance are constant. However, recent studies have shown that atrioventricular compliance may change after an intervention such as balloon mitral valvotomy.[6]

As conversion of analog hemodynamic data to digital format becomes increasingly common and computerized nonlinear regression packages are improved, on-line estimation of MVA from pressure $T\frac{1}{2}$ analysis in the cardiac catheterization laboratory becomes a reality. The purpose of this study was to define the function that gives the best fit for the decay in the mitral pressure gradient to determine whether estimates of MVA can be obtained directly from hemodynamic data.

METHODS

Study group: A total of 61 comparisons of mitral gradient measurements and MVA were made in 37 patients at diagnostic catheterization with 24 comparisons made before and after balloon mitral valvotomy. The mean age of the 30 women and 7 men at diagnostic catheterization was 61 ± 10 years. At the time of the hemodynamic measurements, 30 patients had no mitral regurgitation, 23 had mild (1+), 6 had moderate (2+) and 2 had moderately severe (3+) mitral regurgitation on left ventricular angiography. A total of 47 comparisons were made in normal sinus rhythm, 12 were made in atrial fibrillation, and 2 were made in a ventricular-paced rhythm from a permanent pacemaker. No patient had more than mild (1+) aortic regurgitation seen on Doppler echocardiographic studies completed a mean of

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8.3 ± 12.7 days (median 2.0, range 0 to 56) within cardiac catheterization.

Catheterization protocol: Simultaneous recordings of left atrial and left ventricular pressure were obtained at a paper speed of 100 mm/s with a 7Fr balloon-tipped catheter passed through a transseptal sheath to the left atrium and with a 7Fr pigtail catheter (Cordis) inserted into the left ventricle from the right femoral artery. MVA was estimated from the Gorlin formula using the Fick cardiac output (MVA_{Gorlin}) or the Dexter modification (MVA_{Dexter}).[8]

The catheter system had the following damping characteristics (n = 5): the damped natural frequency, N_D = 11.6 ± 2.9 Hz; damping coefficient, D = 0.62 ± 0.5; and undamped natural frequency, N = 14.4 ± 2.9 Hz.[9] Mitral balloon valvotomy was performed with either single (30 mm) or double (15 to 20 mm) balloons in 24 patients.[10]

Numerical analysis: Left atrial and left ventricular pressure tracings were digitized at 25 ms intervals to yield average values of mitral gradient versus time from 3 (normal sinus rhythm or pacing) or 5 (atrial fibrillation) consecutive beats (Figure 1). All linear and nonlinear regression analyses were performed by fitting gradient versus time data to functions with RS1 (Research and Statistics Management; Bolt, Beranek and Newman, Cambridge, Massachusetts). The computer program uses the technique of nonlinear least-squares parameter estimation for nonlinear functions.[3,11] The method has a convergence criterion of 0.0001. All regressions were subjected to 2 to 25 iterations. Numerical analyses were performed on a VAX 11/780 computer (Digital Equipment Corporation, Maynard, Massachusetts).

Mitral gradient versus time (t) was fit to 4 different functions (Table I). The mitral gradient data (from peak gradient to either the onset of the *a* wave [Figure 1] or ventricular systole) were fit to linear, exponential and parabolic functions. Both the rising and falling components of the mitral gradient were fit to an exponential product.

The slope and parameters of the regression can be used to calculate pressure T½ values. These T½ values correspond to the time taken for the mitral gradient to fall to one-half its initial value along a slope defined by the regression. Linear regression analysis always yields a value for T½; however, in cases where the asymptote of the nonlinear function is >0.5 peak gradient, no real value for T½ is generated (e.g., a negative argument for $\sqrt{}$ or for ln appears in the formulas in Table I). For the mitral gradient data, real T½ values were defined in 85 to 100% of cases.

Converting half-time values to estimates of mitral valve area: T½ values were converted to estimates of MVA after defining a constant term in a manner identical to that used for Doppler echocardiography in which

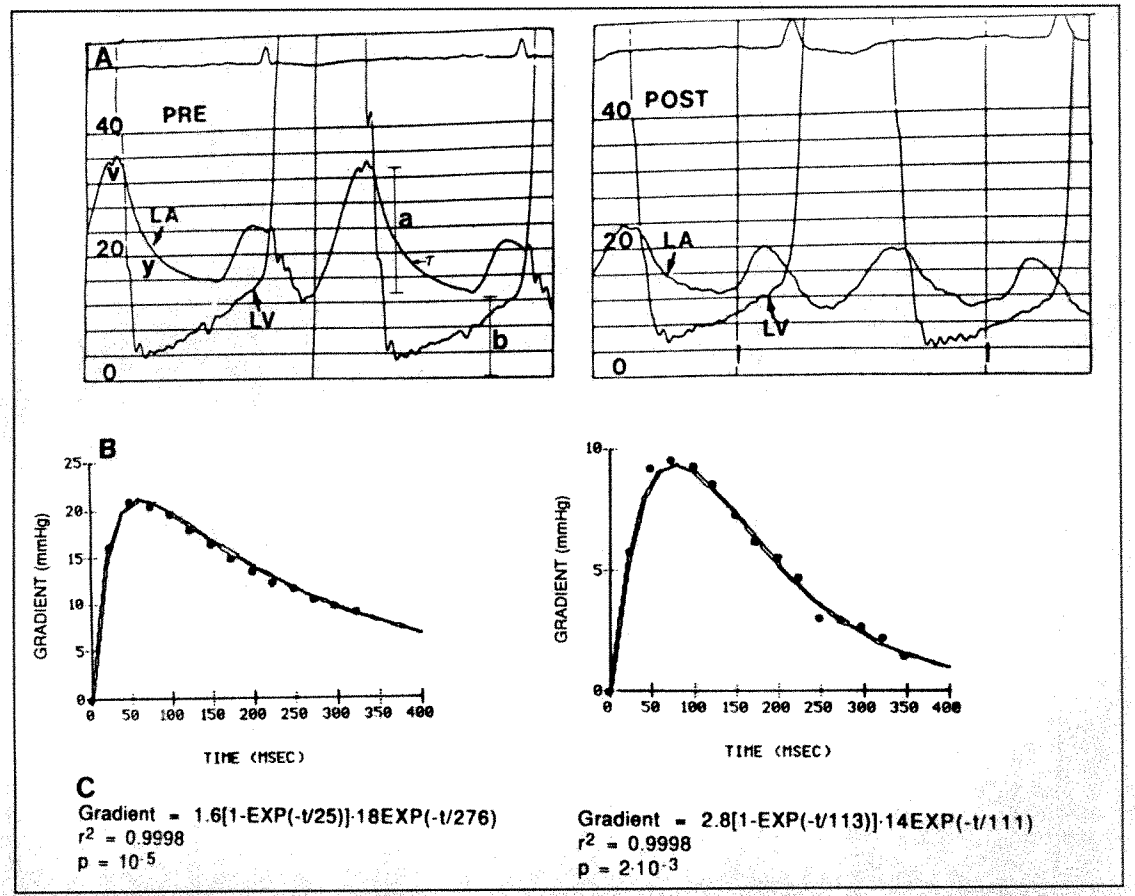


FIGURE 1. ***A*, left atrial (LA) and left ventricular (LV) tracings recorded on 40 mm Hg scale before (PRE) and after (POST) valvotomy, showing v wave, y descent, and examples of the parameters a, τ and b for the exponential fit of the gradient decay. *B*, digitized mitral gradient is well described by the exponential product given in *C*.**

TABLE I Formulas for Regression Analysis and Calculation of Half-Time Values (T½)

Hemodynamic Data	Regression	T½
Mitral gradient		
Linear	$G = at + b$	$T_{1/2} = -\frac{b}{2a}$
Exponential	$G = ae^{(-t/\tau)} + b$	$T_{1/2} = \tau[\ln(2a) - \ln(a - b)]$
Parabolic	$G = (a - t\tau)^2 + b$	$T_{1/2} = \frac{a - \sqrt{\frac{1}{2}(a^2 - b)}}{\tau}$
Exponential product	$G = a[1 - e^{(-t/\tau_1)}] \cdot be^{(-t/\tau_2)}$	$T_{1/2} = -\tau_2 \ln\{1/2[1 - e^{(-t_{peak}/\tau_1)}]\} \cdot e^{(-t_{peak}/\tau_2)}$*

*Where $t_{peak} = \tau_1 \cdot \ln(\tau_1 + \tau_2/\tau_1)$, which is the value for t at peak gradient (i.e., the value of t at which d gradient/dt = 0. This holds only for conditions where $\tau_2 \geq \tau_1$. In all cases the value for T½ for the exponential product function was solved for empirically by iteration with a convergence criterion of 0.0001.

TABLE II Regression Analysis: Goodness-of-Fit Parameters

Type of Regression	r^2	χ^2	No. of Regressions Converging (%)
Mitral gradient			
Linear	0.993 ± 0.010	1.007 ± 1.965 ★	61 (100)
Exponential product	0.987 ± 0.020	0.767 ± 1.039 ★	55 (90)
Exponential	0.994 ± 0.011	0.268 ± 0.283 ★	55 (90)
Parabolic	0.997 ± 0.006	0.225 ± 0.269 ★	56 (92)

★$p < 0.05$ by 2-way analysis of variance and the Scheffe F test for multiple comparisons.

TABLE III Mitral Valve Constants

Type of Regression	Constant, C (ms) Derived from $MVA_{Gorlin} = C/T_{1/2}$
Mitral gradient	
Linear	231 ± 11
Exponential	147 ± 10
Parabolic	156 ± 10
Double exponential	191 ± 8

the relationship — MVA = 220/T½ — has been widely accepted.[7] To accomplish this, we made data sets that related the Gorlin MVA to T½ values from the regressions for mitral gradient decay. By using nonlinear regression analysis, we defined the function:

$$MVA_{Gorlin} = \frac{C}{T_{1/2}}$$

where C is the constant that relates pressure or gradient T½ to estimated MVA.

Statistical analysis: All data are presented as mean ± SD. Goodness-of-fit for the regression analyses was determined by measuring chi-square for each regression, which is a measure of the disagreement between the data set and the regression, adjusts for the number of variables in each expression, and thus allows for direct comparison of different functions for similar data sets.[12] In addition, goodness-of-fit was assessed by measuring r^2, the coefficient of determination.[13] Agreement between the Gorlin measurement of MVA and the regression-derived estimate of MVA was calculated according to the methods of Bland and Altman.[14] Two-way analysis of variance was performed to identify differences among the parameters for goodness-of-fit for the regressions for mitral gradient data: If a significant result was obtained by analysis of variance, the Scheffe F test for multiple comparisons was used to identify significant differences among the individual parameters.[15] One-way analysis of variance was used to assess the effects of mitral regurgitation on the slope of the gradient. Paired *t* test was performed to compare measurements in patients before and after balloon valvotomy. Fisher's z transformation was used for multiple comparisons of the correlation coefficients for the relationships between MVA estimated from the regression analysis and valve area measured by the Gorlin method.[13] A p value <0.05 was considered significant.

RESULTS

Regression analysis of mitral gradient data: Regression analysis permitted linear regressions to be defined for all patients, but nonlinear regressions did not converge in 8 to 10% of the attempts despite as many as 25 iterations (Table II). Chi-square values for the linear regressions were significantly higher, thus describing poorer fits than those for exponential and parabolic functions. Thus, the decay of the mitral gradient is a nonlinear process that can be approximated reasonably well by a linear function.

Correlating pressure half-time values with mitral valve area: Each regression analysis yields a slope for the decay of the mitral gradient that can be used to calculate T½ values. To estimate MVAs from T½ values, we used the Gorlin measurement of MVA and measured the mitral constant C for each type of regression in a manner identical to that used in Doppler echocardiography: $MVA_{Gorlin} = C/T_{1/2}$. The value used in Doppler echocardiography, which is derived from the linear regression of mitral velocity decay, is 220.[7] This is in good agreement with a value of 231 ± 11, which we obtained from linear transformation of mitral gradient

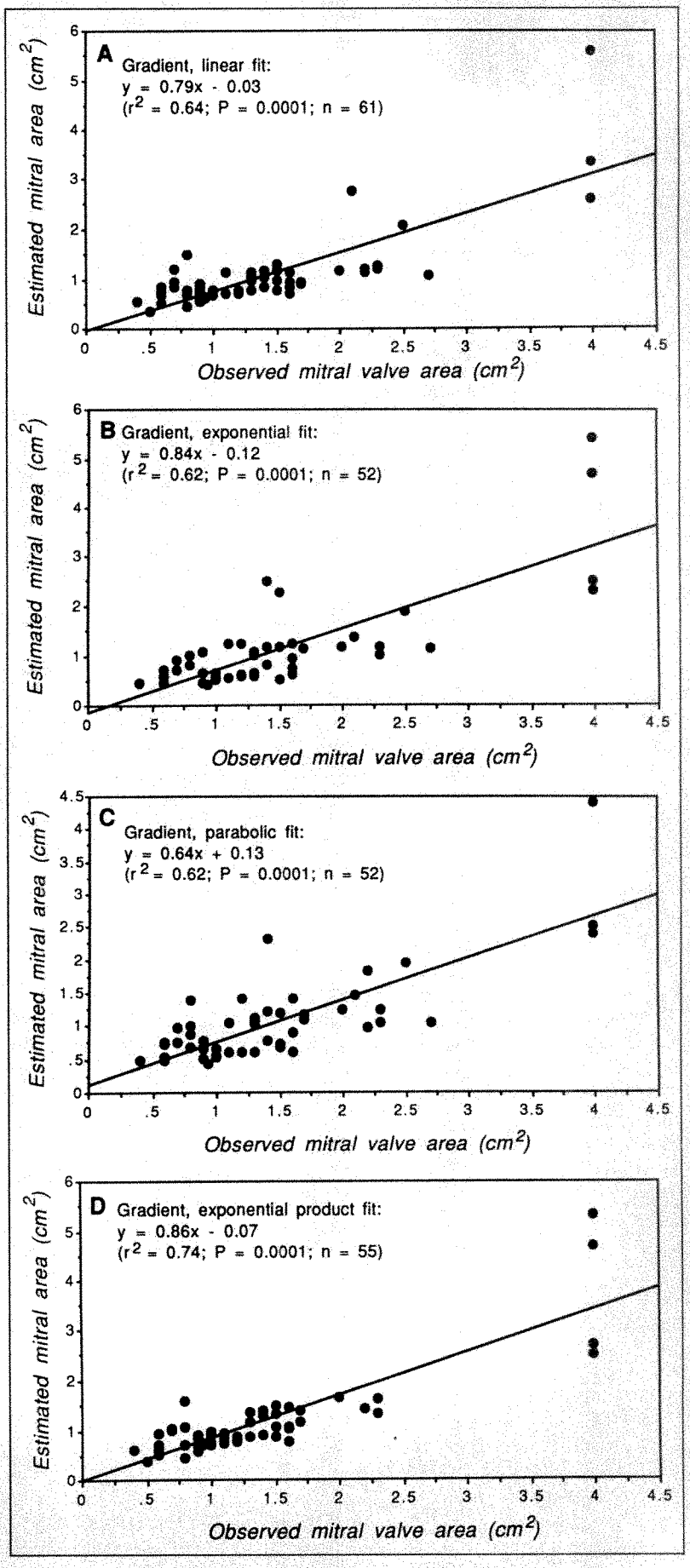


FIGURE 2. Mitral gradient correlations. Correlations between mitral valve area from linear *(A)*, exponential *(B)*, parabolic *(C)* and exponential product *(D)* regressions and mitral valve area measured with the Gorlin formula.

TABLE IV Hemodynamic Parameters Before and After Balloon Valvotomy in 24 Patients

Parameter	Valvotomy	
	Before	After
MVA (Gorlin, cm^2)*	0.8 ± 0.3	1.7 ± 0.5
Cardiac output (liters/min)	3.7 ± 1.0	3.9 ± 1.0
Left atrial pressure (mm Hg)*	27 ± 5	18 ± 6
T 1/2 (ms) and MVA (cm^2) from mitral gradient		
Linear		
T½*	261 ± 89	178 ± 53
$MVA_{regression}$*	0.7 ± 0.2	1.3 ± 0.5
Exponential		
T½*	184 ± 46	124 ± 60
$MVA_{regression}$*	0.7 ± 0.2	1.3 ± 0.6
Parabolic		
T½*	178 ± 52	120 ± 54
$MVA_{regression}$*	0.8 ± 0.3	1.3 ± 0.5
Exp. product		
T½*	221 ± 81	142 ± 39
$MVA_{regression}$*	0.8 ± 0.3	1.4 ± 0.3

*$p \leq 0.005$ by paired t-test.
Exp. = exponential; MVA = mitral valve area.

data (Table III). All 4 types of mitral gradient analyses yielded good correlation between the predicted and measured values of MVA with coefficients of determination (r^2) of 0.62 to 0.74. Using the test for multiple comparisons among correlation coefficients, we observed no significant differences among the correlation coefficients from the 4 methods (Figure 2, A to D), suggesting that linear regression analysis is as good as nonlinear analysis. The regression analyses consistently underestimated MVA. To determine how much the regression estimate differs from the Gorlin measurement, we calculated the precision of the agreement between the 2 methods. For the linear method, we observed that the regression analysis underestimates MVA by 0.33 cm^2 (95% confidence interval: 0.20, 0.46). The exponential method underestimated MVA by 0.36 cm^2 (0.46, 0.77), the parabolic method by 0.39 cm^2 (0.25, 0.53), and the double exponential method by 0.20 cm^2 (0.08, 0.32).

If the values for MVA = 4.0 cm^2 are deleted, the r^2 values range from 0.58 to 0.70 in the correlations shown. Because 31 of 61 patients had at least mild (1+) mitral regurgitation, we also used the Dexter modification of the Gorlin formula to calculate MVA, but found that the agreement between the regression estimates for MVA and the calculated values was not significantly improved (data not shown). If the patients with more than mild (>1+) mitral regurgitation are completely excluded from the analysis, the r^2 values range from 0.59 to 0.75.

The estimates for MVA based on regressions of the mitral gradient showed no correlation to cardiac index ($r^2 = 0.001$ to 0.003).

We observed good correlation between T½ values obtained from linear regression of the Doppler measurements and parabolic transformation of the pressure gradient data ($y = 0.62x + 20.2$; $r^2 = 0.78$; $p = 0.0001$). The regression estimates for MVA were correlated with Doppler measurements of MVA,[7,16] yielding r^2 values that ranged from 0.51 to 0.71. The regression estimates for MVA were also correlated with 2-dimensional echocardiographic measurements of MVA with r^2 values that ranged from 0.56 to 0.73.

Effect of balloon mitral valvotomy on results from regression analysis: Balloon mitral valvotomy was performed in 24 patients, increasing the mean MVA from 0.8 ± 0.3 to 1.7 ± 0.5 cm^2, measured with the Gorlin formula. This was associated with a significant decrease in left atrial pressure, no change in cardiac output, and a significant decrease in T½ values measured from all types of regression analysis of mitral gradient data. In addition, the T½ values generated estimates of MVA after valvotomy that were significantly greater than the preprocedure values (Table IV).

The correlation between predicted valve areas from regression analysis and measured valve areas from the Gorlin formula after valvotomy showed good agreement: linear ($r^2 = 0.46$, $MVA_{regression} = 0.72 \cdot MVA_{Gorlin} + 0.2$, $n = 24$); double exponential ($r^2 = 0.64$, $MVA_{regression} = 1.0 \cdot MVA_{Gorlin} + 0.1$, $n = 19$); exponential ($r^2 = 0.26$, $MVA_{regression} = 0.78 \cdot MVA_{Gorlin} + 0.3$, $n = 21$); and parabolic ($r^2 = 0.26$, $MVA_{regression} = 0.6 \cdot MVA_{Gorlin} + 0.3$, $n = 21$).

DISCUSSION

In this study, we digitized mitral pressure tracings and performed regression analysis in order to define the mathematic equation that most closely fits the observed data. This work derives from the important fundamental modeling of mitral hemodynamics in vitro that has been reported by other investigators with nonlinear regression analysis.[2,4–6,17] The unique aspect of this study was the use of nonlinear regression analysis of clinical hemodynamic data to model the exponential and parabolic processes that are predicted if atrioventricular compliance is constant and viscous or convective resistance predominates, respectively.[2,6] Previous clinical studies have measured pressure T½ directly from left atrial and left ventricular pressure tracings without digitization and regression.[6]

Based on the results presented here, we conclude that approximation of the mitral gradient decay to a linear function is a reasonable alternative to nonlinear regression analysis: Use of the linear approximation is supported by the simplicity of linear regression analysis, the goodness-of-fit assessment, and reliable predictions of MVA from T½ values. However, we observed that the nonlinear functions provided better fit and agreement with the hemodynamic measurement of MVA, which is in support of the fundamental hydrodynamic principles of mitral valve behavior.[3] Both exponential and parabolic functions gave better fits than the linear regression, with a trend in favor of the parabolic function, which is consistent with the experimental work of Flaschkampf[4] and Thomas[5] and their co-workers. In all cases, we observed that the pressure T½ method gives better predictions of MVA before valvotomy than after the intervention, which is consistent with the work of others.[6] However, we continued to observe significant correlations between the predicted and measured MVA

after valvotomy, suggesting that changes in T½ values in a given patient may yield accurate predictions about changes in MVA.

Study limitations: First, the left atrial recordings were made with fluid-filled catheters. Although every effort was made to enhance frequency response by attaching all transducers directly to the catheter manifold ports and by using only single-lumen 7Fr or 8Fr catheters to produce a system with a damped frequency response of about 10 to 20 Hz,[18] higher fidelity tracings could have been obtained with micromanometer-tipped catheters. The use of fluid-filled systems may account for the consistent underestimation of MVA from the analysis of the rate of decay of the mitral gradient seen in this study. This is so since the fluid-filled catheter system underrepresents the peak gradient and hence the rate of decrease in the gradient. The measurement of MVA based on the rate of decay in the mitral gradient will be underestimated. However, cardiac catheterization is routinely performed with fluid-filled catheters; thus, the results of this study have greater potential applicability. Second, the T½ values were subjected to regression analysis with measurements of MVA from the Gorlin formula. Each component of the Gorlin formula is subject to error in measurement so that the final measurement of valve area is associated with the propagation of an error that may be as high as 25%. Although cardiac output calculated from measurements with the Waters metabolic rate meter correlates closely with values from thermodilution (slope = 1.02, r = 0.86), one study showed that the values were uniformly lower than those from other methods by about 20%.[19] In addition, the Gorlin formula itself contains a constant that is influenced by mitral valve geometry,[4] low-flow states[17] and severity of mitral regurgitation. No compensation has been made in this study for the first 2 variables. Since the Gorlin measurements are subject to inaccuracy, we also correlated the results from the regression analysis with Doppler estimates, 2-dimensional echocardiographic measurements, and the Dexter modification of the Gorlin formula to compensate for mitral regurgitation (in which angiographic cardiac output is substituted for Fick cardiac output), and found that the results were unchanged. Even with its limitations, the Gorlin formula is the best formulation available for this type of analysis. Third, this study was not designed to test whether the pressure T½ method may yield information about the MVA that is independent of other hemodynamic variables. Certainly, the T½ values are influenced by cardiac output, left atrial and left ventricular compliance,[6] and mitral orifice shape.[4] Fourth, lack of convergence during regression attempts in certain cases and impossible values, such as the square root or logarithm of a negative number, suggest that the assumptions underlying the nonlinear model are being violated. Thus, the conclusions regarding the actual underlying mechanisms (viscous versus convective resistance) may not be warranted.

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Transcatheter Closure of Atrial Septal Defect by "Buttoned" Devices

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During a 21-month period ending in August 1991, 12 patients underwent transcatheter closure of atrial septal defect (ASD) with a "buttoned" device through an 8Fr sheath, using an institutional review board-approved, custom-made device protocol initially, and Food and Drug Administration-approved clinical trials subsequently. Ten children had left-to-right shunts across the ASD and 2 adults had their patent foramen ovale closed to prevent recurrent paradoxical embolism (including cerebrovascular accidents). The device dislodged in 1 of the 4 patients in whom a first-generation device was used, and retrieval of the device, and surgical closure of the ASD were performed without incident. In the remaining 11 patients (age range 7 months to 45 years, weight 3.6 to 64 kg), the device remained intact, and pulmonary-to-systemic flow ratio decreased from 2.1 ± 0.3 to 1.04 ± 0.06. Follow-up chest x-ray and echo-Doppler studies were available in all patients 0.5 to 18 months after the procedure. The device was intact in all patients. Small residual shunt detected by color Doppler was seen in 2 children. Right ventricular size decreased (23 ± 6 to 17 ± 3 mm; p <0.01), and paradoxical septal motion disappeared in all patients. There was no recurrence of paradoxical embolism in the 2 adults. No complications occurred during follow-up. It is concluded that transcatheter closure of ASD with the buttoned device is feasible, effective and safe, and can be accomplished with small, 8Fr sheaths (even in infants weighing 3.6 kg), follow-up results are excellent, and clinical trials on a larger number of patients are needed.

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Surgical closure of atrial septal defect (ASD) is a conventional treatment option to correct this defect. The mortality rate for surgical correction is low (<1%). However, the morbidity of anesthesia, thoracotomy, cardiopulmonary bypass, and postoperative monitoring in the intensive care unit is considerable. Scar of surgery, and expense are additional disadvantages. Over the last 2 decades, King and Mills and their coworkers,[1–3] Rashkind,[4] and Lock and Rome and their coworkers[5,6] developed transcatheter methods to close ASD. Whereas these methods have advantages over surgical closure, the delivery catheters/sheaths are quite large and bulky, needing 23Fr (King and Mills' device), 16Fr (Rashkind's "hooked" device), and 11Fr (Rashkind's double-umbrella device and clamshell septal umbrella — USCI, Division of Bard, Inc., Billerica, Massachusetts) sheaths to implant the device across the ASD. Sideris et al[7] developed a "buttoned" device that can be delivered by an 8Fr sheath. Use of these devices in animal models[7] and a few human subjects[8–10] has been reported. The purpose of this article is to present our experience with Sideris' device in an attempt to assess safety and efficacy of this system.

METHODS

During a 21-month period ending in August 1991, 12 patients underwent transcatheter closure of ostium secundum ASD with a buttoned device designed by Sideris et al.[7] The study was performed under a protocol for use of the custom-made devices in humans approved by our institutional review board for the first 6 patients. Thereafter, Food and Drug Administration approval for investigational device exemption was sought, during which period, the study was suspended. After an investigational device exemption was issued by the Food and Drug Administration, the study was resumed. Informed consent was obtained from patients or their parents, as appropriate. The cardiac surgery team was on standby during the device implantation, as per the protocol.

Patients were selected on the basis of standard criteria established for surgical treatment of ASD. Only patients with clinical and laboratory features (including echo-Doppler studies) suggesting the need for cardiac catheterization and surgical correction were chosen.

The buttoned device system consists of 3 components: the occluder, counter-occluder and a delivery system. The occluder is made of a Teflon-coated wire skeleton covered with 1/16 inch of polyurethane foam. The wire skeleton is x-shaped when unfolded, and the wires can be made to position parallel for introduction into an 8Fr sheath. A 2 mm string loop is attached to the center of the occluder; the loop is closed by a 1 mm knot

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("button"). In the first-generation device (used in the first 4 patients), the knot was not radiopaque, and in the second-generation device (used in the last 8), a radiopaque marker identifies the position of the button. The counter-occluder is composed of a single-strand, Teflon-coated, wire skeleton covered with a rhomboid-shaped polyurethane foam. A rubber piece is sutured in its center and becomes a "buttonhole." The device delivery system consists of: (1) a Teflon-coated 0.035 inch guidewire (Cook, Inc., Bloomington, Indiana) (the loading wire); (2) a folded 0.008 inch nylon thread passing through the guidewire after having its core removed (loop of thread passes through loop in center of occluder); (3) an 8Fr long sheath (Cordis Corp., Miami, Florida); and (4) an 8Fr multi-A2 (Cordis) catheter (pusher) that is used to advance the occluder and counteroccluder within the sheath.

Patients were sedated with a mixture of meperidine, chlorpromazine and promethazine. This was supplemented with intermittent doses of midazolam to ensure adequate sedation. No general anesthesia was used. Femoral artery pressure, oxygen saturation by pulse oximetry, and heart rate by electrocardiogram were monitored throughout the procedure. Complete cardiac catheterization (including left ventricular cineangiography) was performed to confirm the clinical diagnosis and to exclude other cardiac defects. Probing of all 4 pulmonary veins was performed to ensure their entry into the left atrium. Cineangiography from the right upper pulmonary vein at its junction with the left atrium was performed in a 4-chamber (30° left anterior oblique plus 30° cranial angulation) and a lateral view. Stretched diameter of the ASD was measured by slowly withdrawing progressively larger balloons across the ASD in a manner described by King et al[11] and by us.[12] A stretched diameter >22 mm is generally considered unsuitable for transcatheter closure. During the initial experience, a device that was 15 mm larger than the stretched ASD diameter was chosen for implantation. Currently, we use a device that is at least twice the size of the stretched ASD diameter. After having concluded that device implantation was feasible, we administered heparin intravenously (100 U/kg, maximum 3,000 U).

An 8Fr multi-A2 catheter (Cordis) with an 8Fr long sheath (Cordis) was positioned in the left atrium. The catheter was removed, and the sheath was clamped to prevent back bleeding. Precautions were taken to prevent vacuum creation and air entry during removal of the catheter. The occluder was folded and introduced into the sheath. An 8Fr catheter (pusher) was inserted over the loading wire into the sheath and advanced, pushing the occluder toward the left atrium. When the occluder was at the tip of the sheath, verification that the tip was in the mid-left atrium was obtained by biplane fluoroscopy. While holding the device in the mid-left atrium, the sheath was gently withdrawn, allowing springing open of the occluder; then, the occluder assumed its original shape. The occluder was gently pulled back against the atrial septum, and after it was clear that the occluder did not come through the ASD, the pusher catheter was removed. The counter-occluder was threaded over the loading wire (through the rubber piece, buttonhole) and positioned within the sheath. The pusher catheter was reintroduced into the sheath (over the loading wire) and advanced, pushing the counter-occluder toward the right atrium. The sheath was withdrawn into the mid-right atrium, keeping the occluder in the left atrium. The counter-occluder was then extruded out of the sheath into the mid-right atrium, while it was still on the loading wire. Introduction of the 1 mm knot (button) of the occluder loop through the buttonhole of the counter-occluder was performed by simultaneously (gently) pulling the occluder against the atrial septum while advancing the counter-occluder with the long sheath. Verification that the knot had been pulled through the buttonhole was obtained by fluoroscopy, because of the radiopaque marker on the knot. After satisfactory implantation of the device, the loading wire was cut at the tip and withdrawn, leaving the nylon strands holding the occluder. The device was disconnected by pulling 1 of the 2 nylon strands, thus disconnecting the implanted device from the loading system. During both these maneuvers, the long sheath was gently pressed against the device to prevent inadvertent dislodgement of the device. Fifteen minutes after device implantation, oxygen saturation from the right heart chambers was recorded, and a pulmonary artery cineangiogram was obtained to visualize the adequacy of ASD closure on the levophase of the cineangiogram. Cefazolin (50 to 75 mg/kg) was administered in 3 divided doses. Oral aspirin (5 to 10 mg/kg/day) was begun the day after device implantation to prevent excessive aggregation of platelets on the device. Aspirin was discontinued 3 months later. Two-dimensional echocardiographic and Doppler (pulsed and color) studies were performed on the afternoon of the procedure, and 0.5, 3, 6, and 12 months after transcatheter ASD closure.

Data are expressed as mean ± SD. The Student *t* test was used for comparison of echocardiographic measurements before and after closure. The level of statistical significance was set at $p < 0.05$.

RESULTS

Twelve patients (age range 7 months to 45 years, median 5 years [Table I]) underwent transcatheter closure of the ASD. Two adults had previous cerebrovascular accidents secondary to paradoxical embolism.[13,14] In these patients, ASDs and right-to-left shunting across them with Valsalva maneuver were confirmed by transesophageal contrast echocardiography. The youngest child (aged 7 months, weight 3.6 kg) was born prematurely, had bronchopulmonary dysplasia and absent left pulmonary artery,[9] and had congestive heart failure necessitating closure of the ASD. The first 6 children were previously presented.[9,10] Sex distribution was equal, with 6 in each gender.

The ASD measured 6 to 15 mm on subcostal 4-chamber, 2-dimensional echocardiographic views[12]; in most cases, measurements represent an average of subcostal long- and short-axis images of the atrial septum (Figure 1). Stretched diameter by balloon-sizing[11,12] varied between 10 and 19 mm (mean 14 ± 3). There

TABLE I Data on Patients Undergoing Catheter Closure of Atrial Septal Defect

Pt. No.	Age (yr) & Sex	Weight (kg)	Echo Diameter (mm)	Stretched Diameter (mm)	Qp:Qs Before	Qp:Qs After	Device Size (mm)	Associated Defects/Problems
1	0.58F	3.6	7	10	1.5	1.0	25	Prematurity, BPD, absent LPA, CHF
2	4.0F	17.7	10	13	2.6	1.0	30	0
3	45.0F	50.0	6	14	1.3*	1.0	35	CVA, left axillary artery embolism (paradoxical embolism)
4	6.0M	25.4	8	17	2.0	—	33†	PDA ligated in infancy
5	5.0M	22.8	6	16	1.8	1.0	33	0
6	15.0F	44.0	15	19	2.3	1.1	40	0
7	5.5M	22.0	7.5	13	2.2	1.0	35	Coarctation repaired in infancy
8	4.0F	15.2	10.5	15.5	2.3	1.1	35	0
9	3.0M	16.8	10	16	2.0	1.0	40	0
10	43.0F	64.0	—	13.5	1.0*	1.0	35	CVA, paradoxical embolism
11	3.0M	12.0	7	10	2.0	1.0	30	0
12	1.25M	10.2	—	—	2.0	1.2	30	0

*Adult patients with paradoxical embolism.
†Device dislodged.
BPD = bronchopulmonary dysplasia; CHF = congestive heart failure; CVA = cerebrovascular accident; LPA = left pulmonary artery; PDA = patent ductus arteriosus; Qp:Qs = pulmonary-to-systemic flow ratio.

was left-to-right shunting across the ASD, both on echo-Doppler studies and by oximetry at the time of cardiac catheterization, in all but 1 adult with paradoxical embolism (Table I). The other adult had a small left-to-right shunt with a resultant pulmonary-to-systemic flow ratio (Qp:Qs) of 1.3. Qp:Qs varied between 1.5 and 2.6 (mean 2.1 ± 0.3) in the remaining patients.

The size of the device implanted across the ASD varied between 25 and 40 mm (Table I); in the initial 4 patients, the first-generation device was used, and in the remaining 8, the second-generation device with a radiopaque marker (Figure 2) on the button was used. Implantation of the device was performed in all 12 patients; however, in 1 child (Table I) with a first-generation device, the implanted device dislodged from the ASD site within minutes after placement, and the child was taken to surgery, during which time the device was removed, and the ASD closed.

After device implantation, oxygen saturation data and pulmonary artery cineangiography showed no residual shunt in 8 patients. Small residual shunt with Qp:Qs of 1.1 to 1.2 was observed in 3 children (Table I). Echo-Doppler studies on the afternoon of device implantation showed excellent positioning of the device (Figure 3). Mild, color flow disturbance was observed in 3 children (the same ones with residual shunt by oximetry).

The size of the right ventricle in children decreased from 23 ± 6 to 17 ± 4 mm ($p < 0.02$). In the 2 adults, right ventricular size was initially normal and remained unchanged after closure. Paradoxical motion of the interventricular septum reverted to normal in all patients. All patients were discharged on the day after the proce-

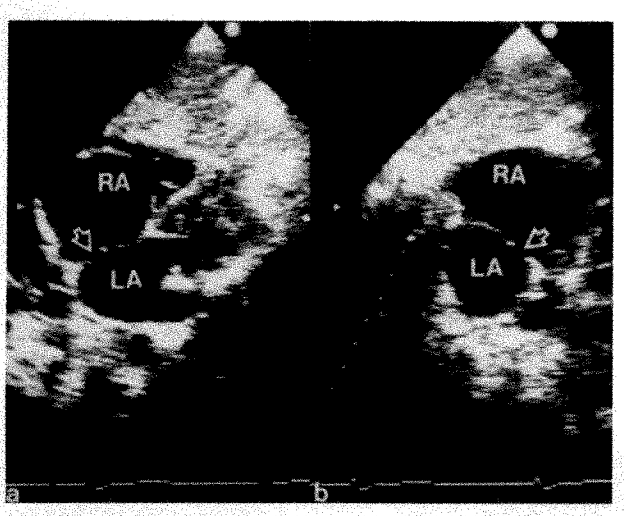


FIGURE 1. Selected video frames from subcostal, 2-dimensional, echocardiographic views of atrial septum in *(a)* long- and *(b)* short-axis views. Atrial septal defect *(open arrow)* is measured in both views and averaged. LA = left atrium; RA = right atrium.

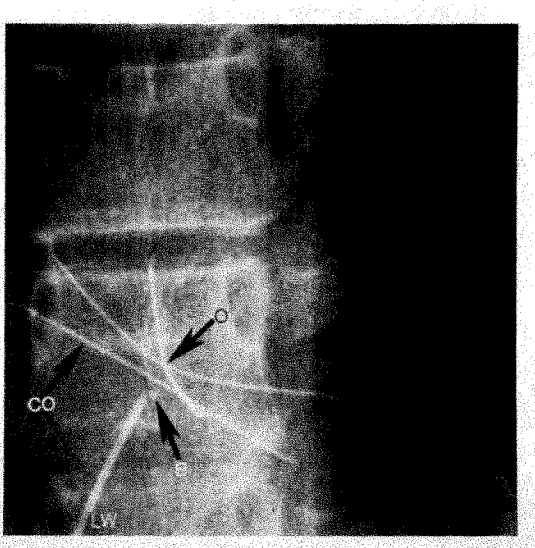


FIGURE 2. Selected cineradiographic frame of device after its implantation, but before disconnecting from the loading wire (LW), showing occluder (O), counter-occluder (CO) and radiopaque "button" (B).

dure. No complications other than the aforementioned device dislodgement occurred.

Follow-up data were available in all patients 0.5 to 18 months (mean 8 ± 6) after the procedure. The device was seen to be in position both on chest roentgenograms and 2-dimensional echographic studies (Figure 3). The size of the right ventricle (mean 17 ± 3 mm) remained unchanged ($p > 0.1$) when compared with that immediately after the procedure by echographic study. There was no paradoxical septal motion in any patient. Small residual shunt detected by color Doppler study was observed in 2 children at follow-up. Neither adult had recurrence of cerebrovascular or any other embolic phenomenon. No complications were observed during follow-up.

DISCUSSION

Feasibility of transcatheter closure of ASD was demonstrated by King and Mills and their coworkers,[1–3] and by Rashkind.[4] However, the device delivery catheters were large and bulky and needed 23Fr and 16Fr sheaths, respectively, for implantation of King et al's[3] interlocking umbrellas, and Rashkind's[4] "hooked" device. However, modified Rashkind's[4] double-disc device could be delivered through an 11Fr sheath. This device was modified by Lock et al[5] (the clamshell septal umbrella® [USCI]), and could also be delivered through an 11Fr sheath. Although much improved, the 11Fr sheath is also too bulky for use in infants and small children. Sideris et al[9] developed a buttoned device that could be delivered to the ASD site through an 8Fr sheath. They initially used this device to occlude experimental ASD in piglets[7] (with success) and subsequently reported their use of it in 3 children.[8] We used the buttoned device in 6 patients.[9,10] This device is small and can easily be delivered through an 8Fr sheath, and we were able to successfully occlude an ASD in a baby weighing 3.6 kg. The small-sized catheter delivery system and the ease with which the device can be implanted across the ASD are definite advantages of Sideris' buttoned device over the other ones.

In the present study, we successfully implanted the device in 12 patients. In 1 child, minutes after the implantation, the device spontaneously dislodged from the ASD site. Inspection of the surgically explanted device revealed that the tie binding the occluder with the counter-occluder was torn. In this child, we used excessive force while buttoning the device. Based on this experience, we modified the device by: (1) strengthening the tie by replacing silk with 4-lb-proof nylon, and (2) introducing a radiopaque marker on the button, so that passage of the buttonhole of the counter-occluder over the button can easily be visualized by fluoroscopy. This modified, second-generation device was used in the last 8 patients. Gentle and simultaneous pulling of the occluder while pushing the counter-occluder with the tip of the sheath is all that is needed, and this buttoning can easily be seen on fluoroscopy. Device dislodgement did not occur after the aforementioned modifications were introduced. Thus, 1 of 4 patients (25%) with the first-generation devices dislodged, whereas of 8 with the second-generation devices, none dislodged ($p < 0.05$).

We used only fluoroscopy during device placement. Hellenbrand et al[15] used transesophageal echocardiographic guidance for device placement, in addition to fluoroscopy. Sideris et al[8] also used this technique in 1 patient. Although there are advantages for transesophageal echocardiographic monitoring, it carries additional risk and prolongs the procedure. Furthermore, general anesthesia is usually needed[15] if transesophageal monitoring is used during device implantation. Because we performed the procedure with a sedative mixture and

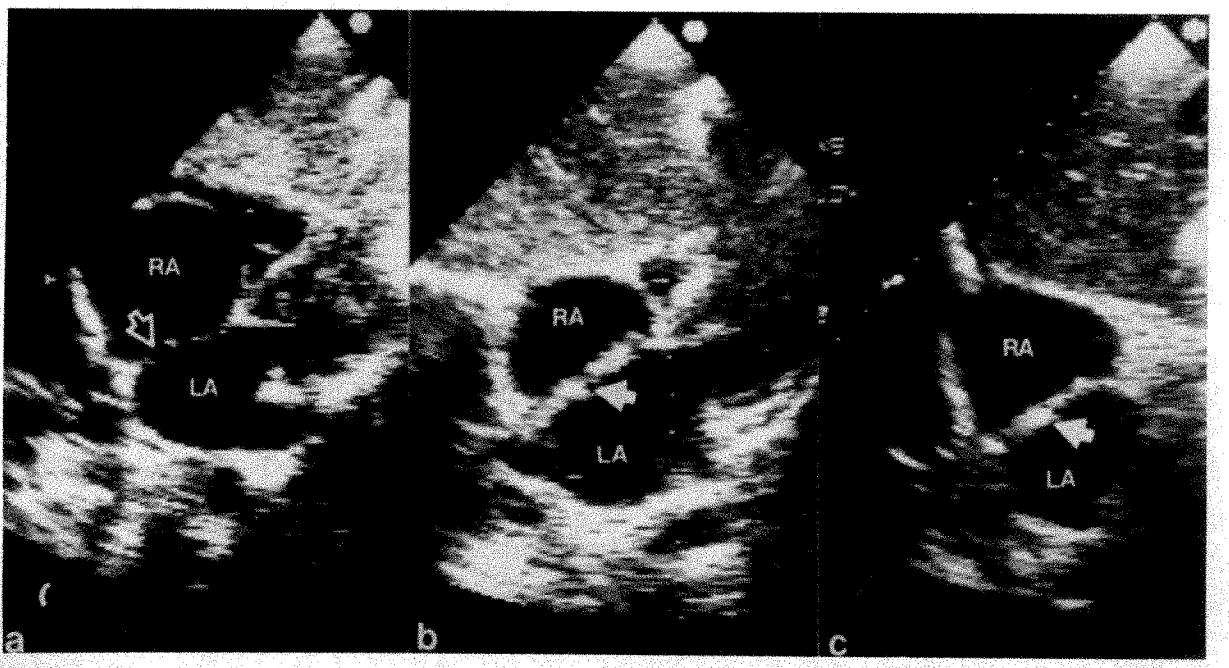


FIGURE 3. Selected video frames from subcostal, 4-chamber, 2-dimensional echocardiographic view of atrial septum *(a)* before and *(b)* immediately after device implantation, and *(c)* at follow-up. Atrial septal defect *(open arrow)* is seen in atrial septum *(a)*, which is completely occluded *(b and c)*. Note device *(closed arrow)* occluding atrial defect. LA = left atrium; RA = right atrium.

local Xylocaine anesthesia, we did not use transesophageal echocardiographic guidance. We believe that fluoroscopy is adequate. However, the advantages and disadvantages with the additional use of transesophageal monitoring are worth investigating in future studies.

Careful transthoracic echocardiography before implantation of the device is necessary to evaluate the size and location of the ASD, and to assure that an adequate rim of atrial septal tissue is present all around the ASD to hold the device in place. Patients with deficient septal rim tissue (Figure 4) are not candidates for transcatheter closure. Final decision to implant the device should be made after balloon-sizing of the ASD.[11,12] Adult patients may need a transesophageal study to evaluate these issues before attempting transcatheter closure.

Decrease in the size of the right ventricle, and reversion back to normal of the paradoxical septal motion immediately after transcatheter ASD closure and at follow-up are suggestive of rapid ablation of the atrial shunt. Small residual shunts at follow-up were seen in 2 children, but without right ventricular volume overloading; whether these will eventually close spontaneously should be determined during further follow-up studies.

In 2 adult patients with paradoxical embolism resulting in cerebrovascular accidents, the ASD was closed successfully. During follow-up, no further embolic episodes were noted. Rome et al[6] reported transcatheter closure in 2 such patients. Although there is no general consensus,[16] some investigators[17,18] recommended surgical closure of the foramen ovale. Now that the transcatheter closure method is available, this may be an effective alternative to surgical closure.

Transcatheter closure of the ASD is gaining wider acceptance as an alternative to surgical closure. The small-sized device delivery system and the ease of implantation of the buttoned devices may have advantages compared with other devices needing a larger delivery

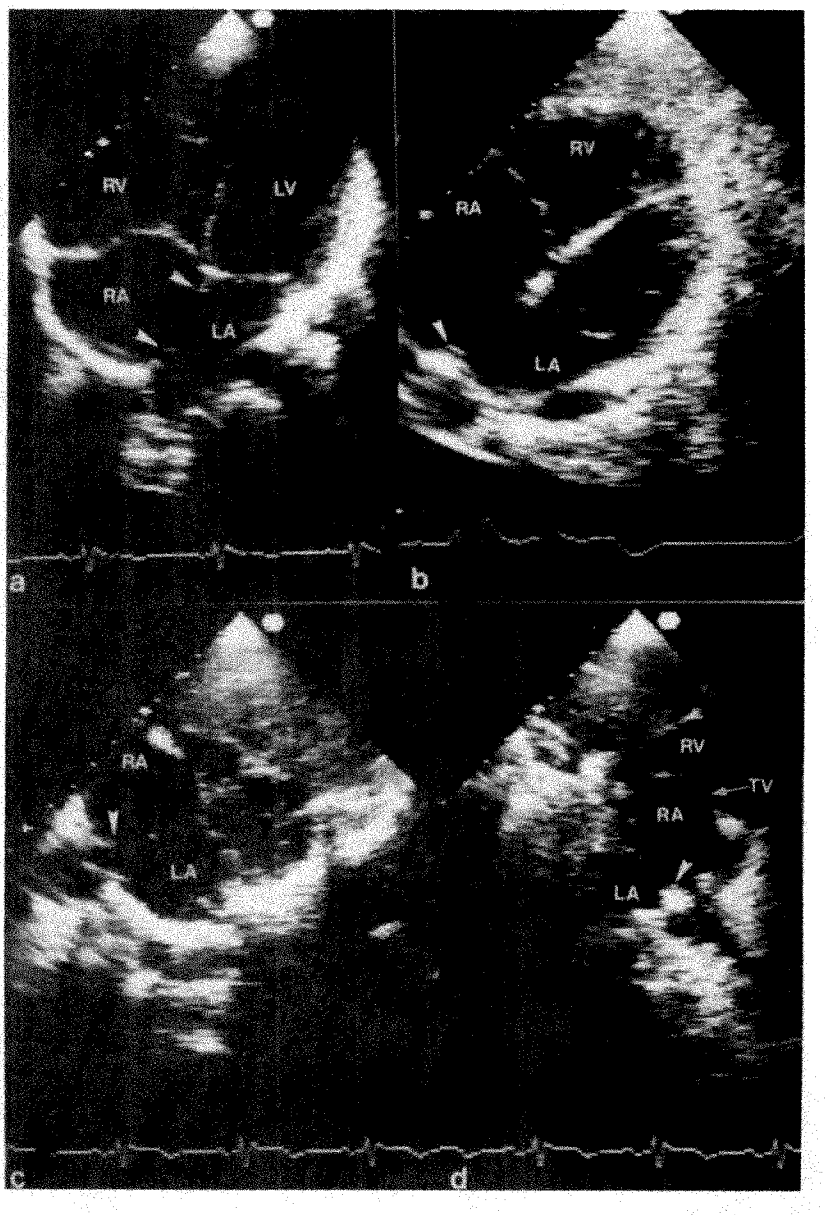


FIGURE 4. ***(a)*** **Apical and** ***(b)*** **subcostal, 4-chamber view of atrial septum showing deficient atrial septal tissue** ***(arrows).*** **Subcostal, 4-chamber view of atrial septum in** ***(c)*** **long- and** ***(d)*** **short-axis views of atrial septum also showing deficient septum in different patient.** ***Solid arrow heads*** **show diminutive atrial septal rims. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; TV = tricuspid valve.**

sheath. It is concluded that transcatheter closure of the ASD with the buttoned device is safe and effective, especially with the second-generation device, and can be accomplished with small (8Fr) sheaths (even in infants weighing 3.6 kg), and clinical trials on a larger number of patients with this device are needed.

Acknowledgment: We wish to express appreciation to E.B. Sideris, MD, for demonstrating the procedure in animal models and children.

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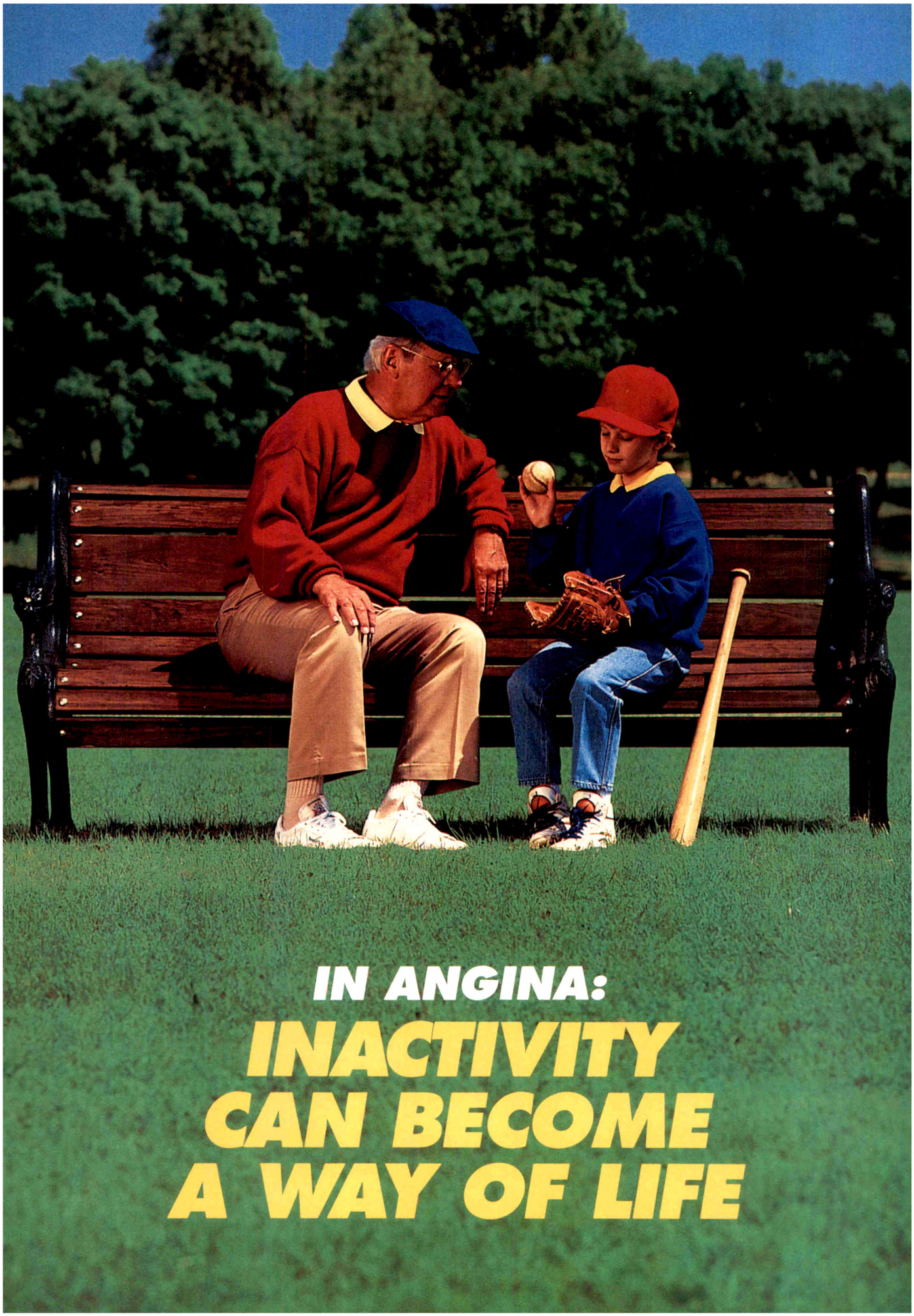
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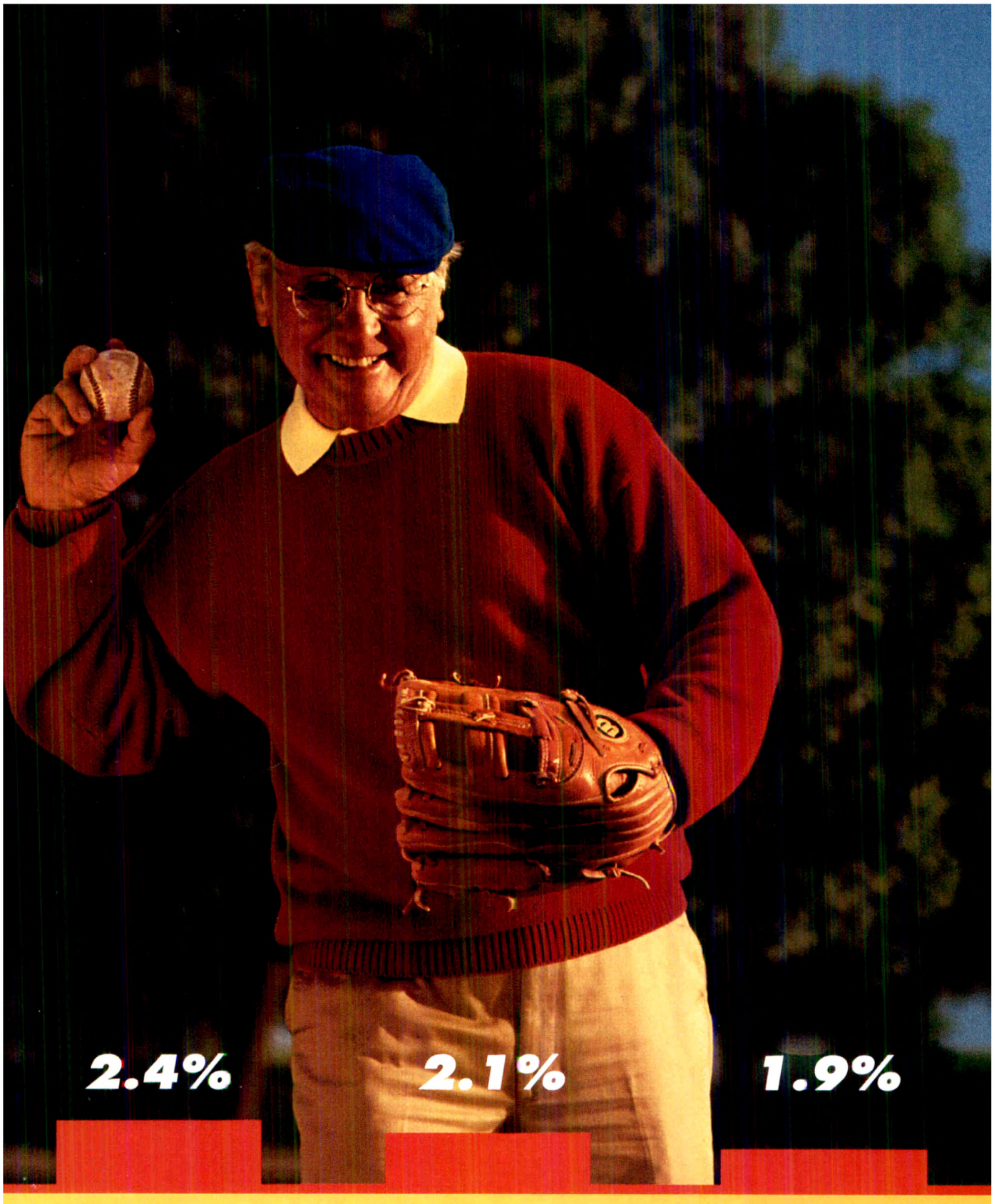
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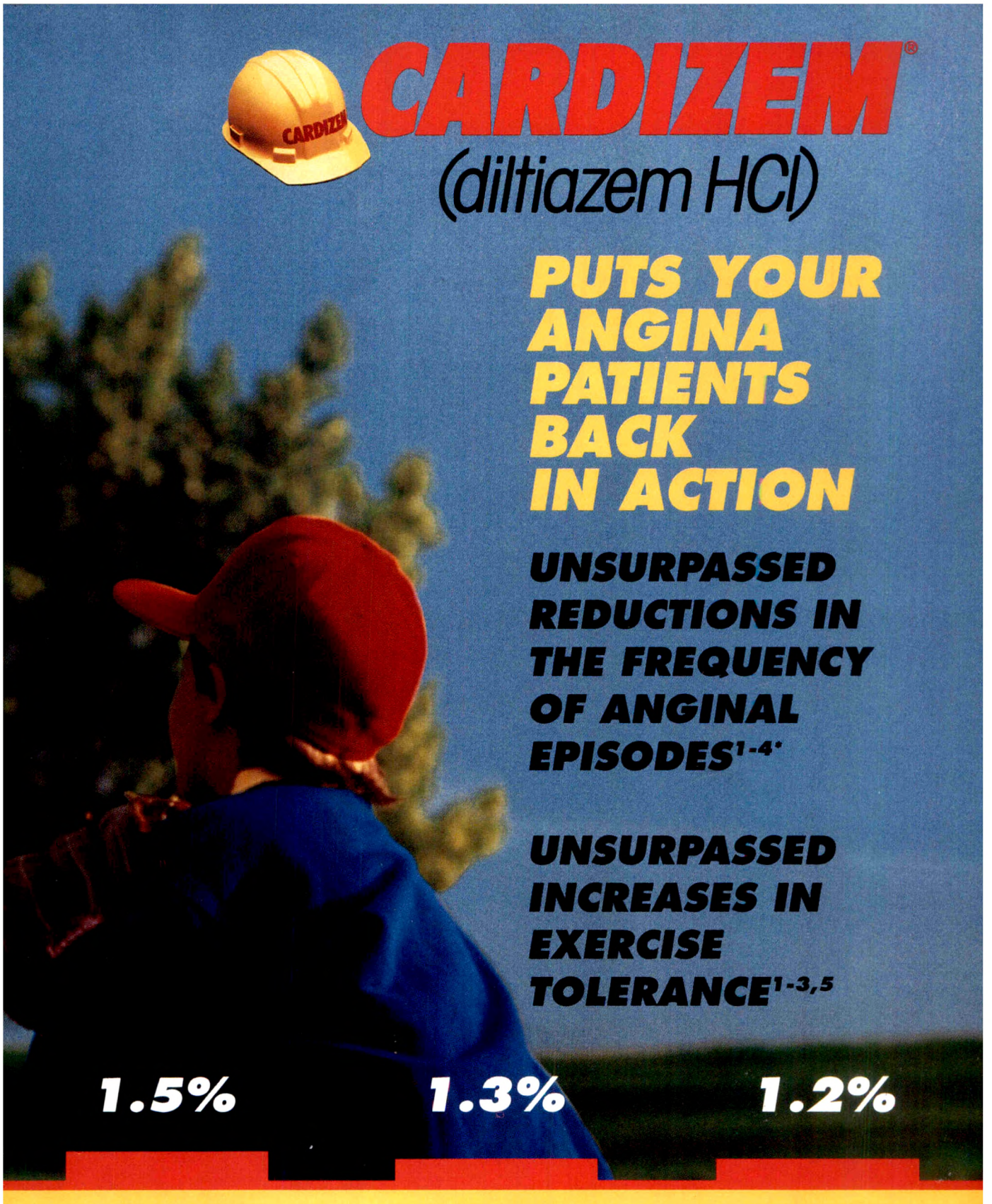


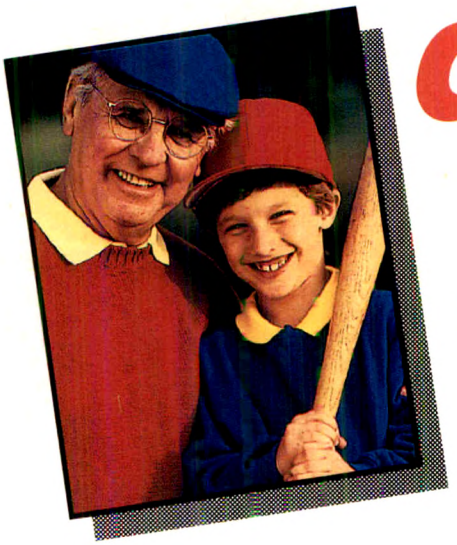
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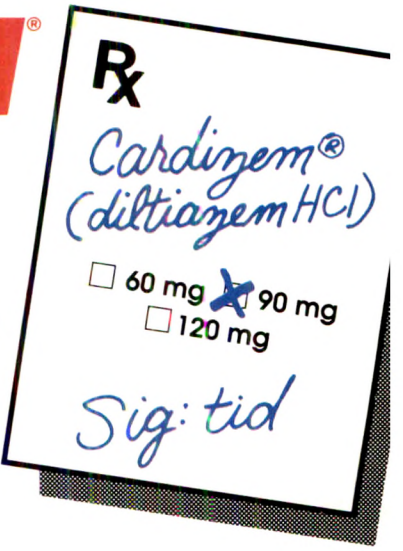
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CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences from these studies, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

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Reversal of Endothelin-1-Induced Vasoconstriction by Nifedipine in Human Resistance Vessels in Vivo in Healthy Subjects

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The influence of blockade of voltage-operated calcium channels by nifedipine on endothelin-1-induced vasoconstriction was investigated in 10 healthy volunteers. Brachial artery infusions of nifedipine (0.25, 0.5, 1 and 3 μg/min/100 ml forearm tissue) resulted in dose-dependent increases (mean ± SD) in forearm blood flow (103 ± 63% to 833 ± 426%). Intraarterial infusions of endothelin-1 (50 ng/min/100 ml) resulted in transient increases in forearm blood flow (2.6 ± 0.9 vs 3.9 ± 2.0 ml/min/100 ml, p <0.01) in the first minute of infusion and subsequent decreases (to 1.0 ± .5 ml/min/100 ml, p <0.01) in the third minute of infusion. Endothelin-1-induced vasoconstriction was reversed by the lowest dose of nifedipine, whereas the higher dosages of nifedipine further increased forearm blood flow to 12.5 ± 6.4 ml/min/100 ml. The percent increase of forearm blood flow during co-infusion of endothelin-1 and the highest dosage of nifedipine was significantly greater compared with nifedipine alone (1,204 ± 531% vs 833 ± 426%, p <0.05). The results demonstrate a dual action of luminally applied endothelin-1 in human resistance vessels in vivo (e.g., transient initial vasodilation followed by pronounced vasoconstriction) and suggest that blockade of voltage-operated calcium channels can effectively counteract the vasoconstrictor effects of endothelin-1.

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Human endothelial cells produce and release the 21-amino acid peptide endothelin-1[1,2] which has potent and long-lasting vasoconstrictor activity in nonhuman[3,4] and also in human arteries and veins in vitro.[5,6] The mechanisms underlying endothelin-1-induced vasoconstriction are not entirely clear.[7] In particular, there is controversy with respect to the involvement of voltage-operated calcium channels since organic calcium antagonists in some studies inhibited endothelin-1-induced vasoconstriction[1,6] but had no substantial influence in others.[3,5,8] There is also evidence that endothelin-1 induces vasodilatation,[4,9] possibly through endothelial release of prostacyclin[10,11] or endothelium-derived relaxing factor.[10] Data on the vascular effects of endothelin-1 in humans in vivo are scarce,[12,13] but it has been shown that the vasoconstrictor response of human resistance vessels to brachial artery infusions of endothelin-1 in healthy volunteers can be effectively blocked by co-infusion of high dosages of either nifedipine or verapamil.[14] Thus, there are considerable discrepancies regarding the reversibility of the vasoconstrictor effects of endothelin-1 by calcium antagonists. Because of increasing evidence that endothelin-1 may be of importance in a variety of cardiovascular disorders,[15–19] the present study was designed to further analyze the dependence of endothelin-1-induced vasoconstriction on the activity of voltage-operated calcium channels in humans in vivo.

METHODS

Subjects: Ten healthy, normotensive (casual sitting blood pressure <140/90 mmHg) volunteers (6 men and 4 women), aged 21 to 44 years (mean 29.6), participated in the study. The study protocol was approved by the hospital ethical committee on the use of human subjects in clinical investigations and all subjects gave written informed consent.

Forearm blood flow measurements: Forearm blood flow was measured bilaterally by venous occlusion plethysmography. Details of the technique have been described elsewhere.[20] In short, a mercury-in-Silastic strain gauge was placed at the upper third of the forearm, which rested comfortably on a support slightly above the level of the heart. The strain gauge was coupled to an electronically calibrated plethysmograph (EC3, Hokanson, Issaquah, Washington). Venous occlusion was achieved by a blood pressure cuff applied proximal to the elbow and inflated to 40 mm Hg by a rapid cuff inflator (EC10, Hokanson). The hand was excluded from circulation by inflating a pediatric blood pressure cuff placed around the wrist to 50 mm Hg above systolic pressure 1 minute before and during fore-

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arm blood flow measurements. Experiments were done on the left (experimental) forearm, while blood flow measurements on the right arm served as a control. Plethysmographic recordings were analyzed using a digitizing board and a suitably programmed computer. The mean value of 4 to 6 recordings obtained within 1 minute was taken for statistical evaluation. Forearm vascular resistance was calculated by dividing mean arterial pressure by forearm blood flow and is expressed as arbitrary units. Heart rate was monitored from the electrocardiogram.

Preparation of solutions for infusions: The forearm volume of each subject was measured by water displacement, and drug doses were adjusted accordingly. All solutions were freshly prepared before each study. Endothelin-1 (Ciba-Geigy, Basel, Switzerland) was diluted in Physiogel (4% gelatin solution, molecular weight 22,000, Swiss Red Cross, Berne, Switzerland) to avoid binding to syringes or tubing. Infusions of Physiogel at volumes of up to 6 ml/min have been shown not to influence forearm blood flow to a measurable degree.[21] Nifedipine was administered using commercially available (Bayer, Leverkusen, Federal Republic of Germany) black-coated syringes and tubing for light protection. Intraarterial infusions were performed with volumes between 0.5 and 2.0 ml/min using a constant speed infusion pump (Sage Instruments Inc., Syracuse, New York).

Study protocol: All studies were performed in the morning with the subjects recumbent and comfortably resting after a light breakfast. All subjects had been asked to refrain from smoking cigarettes and drinking caffeinated beverages for 8 hours before the study; no subject was taking any medicine. The studies were performed in a quiet, air-conditioned room at an ambient temperature of 20 to 22°C and lasted for approximately 4 hours. Under local anesthesia (lidocaine 1%) an 18 gauge catheter (Abbocath-T, Abbott, Sligo, Ireland) was inserted into the left brachial artery for regional drug infusion and recording of arterial pressure using a Statham P23 Pb pressure transducer. The subjects were allowed to rest for 30 minutes after completion of instrumentation before basal forearm blood flow, intraarterial blood pressure and heart rate were recorded. Next, nifedipine was infused into the left brachial artery in 4 dosages (0.25, 0.5, 1, and 3 μg/min/100 ml forearm tissue for 3 minutes each) and forearm blood flow measured in the third minute of each infusion. The dosages were chosen based on a previous study demonstrating that they produced regional vasodilation without systemic hemodynamic effects.[22] After completion of nifedipine infusions, forearm blood flow was allowed to return to control levels. Next, endothelin-1 was infused in a dose of 50 ng/min/100 ml over 3 minutes and forearm blood flow measured throughout the infusion period. This regimen was chosen based on previous observations that this dose on average caused a 50% reduction of resting forearm blood flow in normal volunteers[14] and that little further vasoconstriction occurred between the third and fifth minute of endothelin-1 infusion. Subsequently, the brachial artery infusions of nifedipine (0.25, 0.5, 1, and 3 μg/min/100 ml) were repeated during co-infusion of endothelin-1 (50 ng/min/100 ml) and forearm blood flow measured in the third minute of each combined infusion.

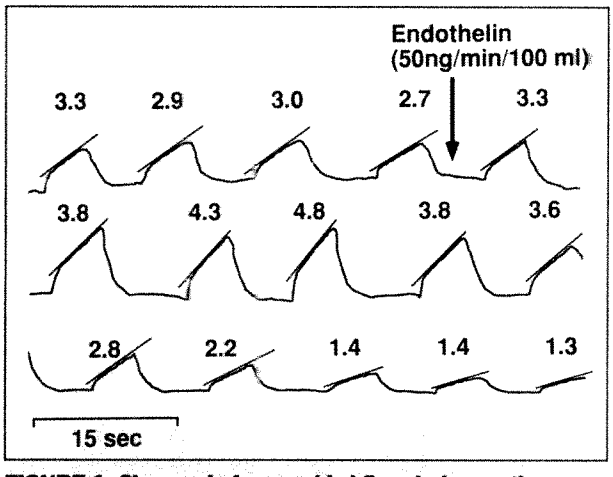


FIGURE 1. Changes in forearm blod flow during continuous brachial artery infusion of endothelin-1 in a healthy volunteer. *Numbers* denote individual forearm blood flow values (ml/min/100 ml forearm tissue). Note the transient increase in forearm blood flow followed by vasoconstriction.

Statistical analysis: Results are expressed as mean ± SD. Analysis of variance for repeated measurements was used to evaluate the time course of endothelin-1 and nifedipine effects on forearm blood flow. The *t* test for paired observations was used to compare results obtained after a particular intervention with the corresponding control values. For evaluation of the effects of nifedipine on endothelin-1-induced vasoconstriction, percent changes from the corresponding control values were used. A 2-tailed p value <0.05 was considered to indicate a significant difference. All calculations were performed using the StatView II (Abacus, Berkley, California) statistical program.

RESULTS

None of the subjects experienced subjective or objective side effects during endothelin-1 infusions and none of the interventions resulted in measurable changes in blood pressure, heart rate or contralateral forearm blood flow. Thus, changes in blood flow in the experimental arm directly reflected changes in vascular resistance attributable to a particular intervention. The time course of changes in forearm blood flow changes during endothelin-1 infusion in one subject is depicted in Figure 1. Endothelin-1 caused an early and transient vasodilator effect which peaked in the first minute. Subsequently, vasoconstriction with a reduction in forearm blood flow ensued. On average, forearm blood flow increased 46% (2.6 ± .9 to 3.9 ± 2.0 ml/min/100 ml ($p < 0.01$) in the first minute of endothelin-1 infusion and decreased 60.8% (to 1.0 ± 0.5 ml/min/100 ml) in the third minute (Figure 2). Brachial artery infusions of nifedipine alone resulted in dose-dependent increases in forearm blood flow from a control value of 2.1 ± 0.76 to 17.9 ± 7.9 ml/min/100 ml. The same infusions during co-infusion of endothelin-1 resulted in an increase from 1.0 ± 0.5 to 12.5 ± 6.4 ml/min/100 ml. The lowest dose of nifedipine, which alone increased forearm

blood flow by 103 ± 63%, completely reversed the reduction in forearm blood flow induced by endothelin-1 (1.0 ± 0.5 vs 2.4 ± 1.1 ml/min/100 ml). A comparison of percent changes in forearm blood flow in response to nifedipine alone and in combination with endothelin-1 (Figure 3) indicated that nifedipine increased forearm blood flow to a similar extent whether or not endothelin-1 was present and that the highest dose of nifedipine in combination with endothelin-1 resulted in greater changes of forearm blood flow compared with nifedipine alone (1,204 ± 531% vs 833 ± 426%, $p < 0.05$).

DISCUSSION

The present study demonstrates that endothelin-1 has a dual action on human resistance vessels in vivo (e.g., a sizable but transient initial vasodilator effect and a subsequent marked vasoconstrictor effect). The pattern of initial vasodilatation and subsequent vasoconstriction is similar to that observed in a conscious dog model[23] and would be compatible with the contention that luminally administered endothelin-1 first has to be taken up into the endothelium where it may rapidly release both prostacyclin[10,11] or endothelium-derived relaxing factor, or both.[10] After passage through the endothelium the peptide eventually leads to smooth muscle contraction that, in the dosage given, overrides the vasodilator effect resulting in marked vosoconstriction. The study also demonstrates that endothelin-1-induced vasoconstriction is effectively counteracted by blockade of voltage-operated calcium channels. Thus, brachial artery infusions of ascending dosages of nifedipine completely abolished the vasoconstrictor effects of endothelin-1, leading to further, pronounced vasodilatation for the higher dosages of the calcium antagonist. Although forearm blood flow did not increase to the same absolute level during infusion of both endothelin-1 and nifedipine compared with nifedipine alone, the relative increase during endothelin-1 co-infusion was statistically greater for the highest dose of nifedipine. Thus, the present study confirms previous observations that blockade of voltage-operated calcium channels reverses endothelin-1-induced vasoconstriction[14] and extends that finding to the fact that lower dosages of a calcium antagonist than used before appear to be effective. Whereas a dose of 6 μg of nifedipine/min/100 ml forearm tissue was used previously[14] the lowest dose in the present study was 0.25 μg/min/100 ml. We did not measure forearm plasma nifedipine concentrations in this study. However, approximate plasma concentrations can be estimated from flow and infusion rate, e.g., 250 ng nifedipine/min/100 ml tissue and a corresponding plasma flow of approximately 3 ml/min/100 ml tissue for the lowest nifedipine dose. This would result in plasma concentrations in the range of 80 ng/ml, values only slightly above those described in some hypertensive subjects after administration of oral nifedipine.[24] Because this dose of nifedipine already completely reversed the vasoconstrictor effect of endothelin-1, it is suggested that similar findings might be obtained during oral administration of a calcium antagonist. Even though our results suggest effective inhibition by blockade of voltage-operated calcium channels of vasoconstriction induced by luminally administered exogenous endothelin-1, it remains to be seen whether this applies also to oral administration of calcium antagonists, to vascular effects of endogenously released endothelin-1 and to vascular beds other than the musculocutaneous vessels of the forearm.

Our findings have some bearing on the proposed mechanisms of action of endothelin-1 and, possibly, may shed additional light on therapeutic aspects of cardiovascular therapy with calcium antagonists. The sequence of events whereby endothelin-1 leads to vascular muscle contraction is not entirely clear, and differences between species and vascular beds investigated have to be considered.[7] However, endothelin-1-induced vasoconstriction appears to involve a component sensitive to blockade of voltage-operated calcium ion channels[7,25] as well as a component that is not.[7,26] The nonblockable component is associated with an increase in intracellular free cytosolic calcium through activation of phospholipase C or protein kinase C, or both, leading to increased phosphoinositol turnover. The resulting membrane depolarization appears to activate voltage-operated, calcium antagonist blockable L-type calcium ion channels leading to sustained contractions. It has also been shown

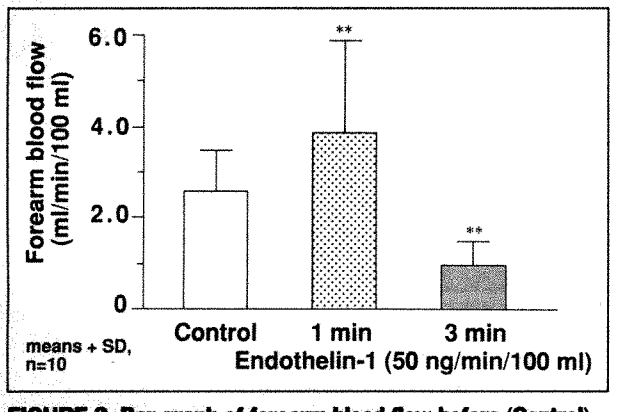


FIGURE 2. Bar graph of forearm blood flow before (Control) and during the first and third minute of brachial artery infusions of endothelin-1 in 10 healthy volunteers. **p <0.01 vs Control.

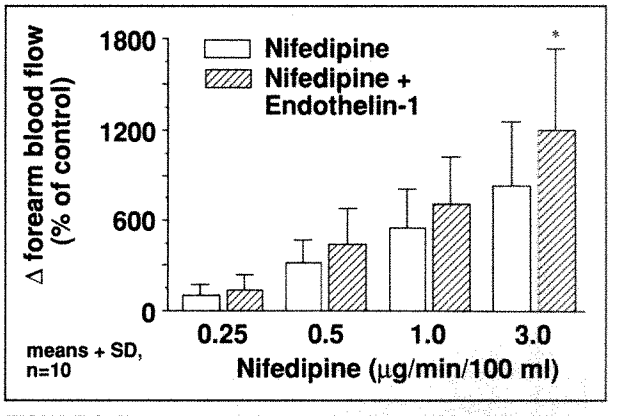


FIGURE 3. Bar graph of changes in forearm blood flow in response to brachial artery infusions of nifedipine alone and in combination with endothelin-1 (50 ng/min/100 ml) in 10 healthy volunteers. Values are percent changes from the corresponding preinfusion values. *p <0.05, nifedipine vs nifedipine + endothelin-1.

that the development of vascular tone depends more on calcium influx through slow calcium ion channels in small rather than large arteries.[26] Even though the initiation of the cascade of events leading to sustained vasoconstriction may not be related to activation of voltage-operated calcium ion channels, it is therefore conceivable that the marked dependence of vascular tone on the activity of voltage-operated calcium ion channels may account for the abolition of sustained endothelin-1-induced vasoconstriction in resistance vessels as observed in this study and also in human mesenteric resistance vessels in vitro.[6]

The physiologic role of endothelin-1 is not known and plasma levels in healthy volunteers are low.[12,17] However, elevated endothelin-1 plasma concentration has been described in a variety of cardiovascular disorders such as acute renal failure,[15] acute myocardial infarction and cardiogenic shock,[16] severe hypertension[17] and human atherosclerosis.[19] It is interesting to note in this context that doubling of plasma endothelin-1 concentrations in dogs resulted in marked increases in vascular resistance, particularly in the renal vasculature,[27] a finding which might indicate that increased endothelin-1 levels play a pathophysiologic role in these conditions. There is also growing evidence that endothelin-1 may play a role in the development of coronary vasospasms.[18] Interestingly, calcium antagonists are remarkably effective in a number of these conditions such as severe hypertension[28] or coronary vasospasm.[29] Inasmuch as elevated plasma endothelin-1 concentrations in these conditions reflect a causal relation it is conceivable that part of the beneficial effects of calcium antagonists may be accounted for by an interference with endothelin-1-induced vasoconstriction. Endothelin-1 also has mitogenic properties in vascular muscle,[30] and endothelin-1 like immunoreactivity has been found in vascular muscle of human atherosclerotic vessel.[19] Although the effects of calcium antagonists on endothelin-1-induced mitogenesis have not been examined, it is tempting to speculate that the postulated antiatherosclerotic effects of calcium antagonists in humans[31,32] may be at least partly attributable to an interference with the peptide's smooth muscle proliferative effects.

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Left Ventricular Dimensions and Mass Using Magnetic Resonance Imaging in Female Endurance Athletes

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Few published studies of left ventricular (LV) mass in female endurance athletes have been performed with M-mode echocardiography, which involves assumptions of LV geometry. Therefore, magnetic resonance imaging, a 3-dimensional technique, was used to examine LV mass, LV end-diastolic volume and mean wall thickness in female long distance runners (n = 13; mean age 29 years), cyclists (n = 12; mean age 26 years) and cross-country skiers (n = 11; mean age 24 years), and the findings were compared with sedentary control subjects (n = 10; mean age 27 years) matched for height and body weight. The physical characteristics for all subjects included height (mean 166 cm, and body weight (mean 56 kg). The percent body fat (mean 11.7) and maximal oxygen uptake ($\dot{V}O_2$max, mean 63 ml · kg^{-1} · min^{-1}) were similar (p >0.05) among all athletic groups, but significantly different from the control group (body fat, mean 22.5%; $\dot{V}O_2$max, mean 35 ml · kg^{-1} · min^{-1}). LV mass (mean 159 kg), LV end-diastolic volume (mean 122 ml), and mean wall thickness (mean 11.5 mm) were also similar among the athletic groups and significantly larger than the following control values: LV mass (mean 115 g), LV end-diastolic volume (mean 93 ml) and mean wall thickness (mean 9.8 mm). Ratios of LV mass to lean body weight were similar among all athletic groups, although athletic groups had larger ratios (p <0.05) than the sedentary control subjects. LV mass/LV end-diastolic volume ratio was similar (p >0.05) among all groups. Our findings indicate that LV mass, LV end-diastolic volume and mean wall thickness are greater in endurance athletes than sedentary control subjects and that the increase in LV mass is proportional to the increase in LV end-diastolic volume.

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Prior studies involving predominantly male subjects and using echocardiography have investigated whether endurance trained athletes have increased left ventricular (LV) mass compared with sedentary subjects.[1–6] Echocardiographic studies of LV mass in female athletes are few in number and include the evaluation of small groups.[7–12] Only Mickelson et al[8] examined the relationship between LV mass and LV end-diastolic volume in female athletes. Moreover, the validity of echocardiographic studies have come into question since they involve assumptions of LV geometry and the conversion of 1-dimensional data to mass measurements.[2,6,13]

As demonstrated by Keller[14] and Katz[15] and their co-workers, magnetic resonance imaging has been shown to be a highly accurate and reliable method for determining LV mass. Magnetic resonance imaging has been used in our laboratory to examine LV mass of elite male endurance athletes.[16] Therefore, this present study was designed to continue these efforts by using magnetic resonance imaging to evaluate LV mass, LV end-diastolic volume and mean wall thickness in female endurance athletes and in sedentary control subjects matched for height, body weight and body surface area.

METHODS

Subjects: Thirty-six female endurance athletes and 10 sedentary control subjects participated in this investigation. The nature and purpose of the study and the risks involved were explained to all subjects, and each signed an informed consent form before participation. The study had been approved by the Institutional Review Board at University of Texas Southwestern Medical Center. The endurance athletes consisted of 13 long distance runners, 12 cyclists, and 11 cross-country skiers. The long distance runners had all run a 10 km race in ≤38:00 minutes within the last 2 years. The cyclists were category 3 or better racers, as designated by the United States Cycling Federation. The cross-country skiers were women who consistently placed in the top 20 in national races. The 10 sedentary control subjects consisted of women who had not participated in any organized sport and who had not engaged in any regular conditioning program for at least 2 years before testing.

Anthropometry and tests: The percentage of body fat was calculated from body density according to the Brozek formula[17] as determined by hydrostatic weighing. Lean body weight was calculated as total body weight minus fat weight. Body surface area was ob-

TABLE I Subject Characteristics

Variable	Long-Distance Runners (n = 13)	Cyclists (n = 12)	Cross-Country Skiers (n = 11)	Sedentary Controls (n = 10)
Age (yr)	29 ± 2	26 ± 2	24 ± 3*	27 ± 6
Height (cm)	169 ± 5	165 ± 5	166 ± 5	165 ± 5
Body weight (kg)	54 ± 4	58 ± 4	59 ± 5	56 ± 7
Body surface area (m^2)	1.61 ± 0.08	1.63 ± 0.08	1.65 ± 0.08	1.60 ± 0.10
Body fat (%)	9.8 ± 2.2	13.7 ± 3.5	11.9 ± 3.5	22.5 ± 5.9†
Lean body weight (kg)	49 ± 4	50 ± 3	52 ± 4*	43 ± 3†

*Significantly different from long-distance runners ($p < 0.05$).
†Significantly different from long-distance runners, cyclists and cross-country skiers ($p < 0.05$).
All values are mean ± SD.

tained from tables based on height and body weight using the equation of Dubois.[18]

Maximal aerobic power ($\dot{V}O_2max$) was determined on either a treadmill, a cycle ergometer, or a Schwinn Airdyne ergometer. The peak $\dot{V}O_2$ obtained during each test was taken as $\dot{V}O_2max$. In the long distance runners, cross-country skiers and sedentary control groups, $\dot{V}O_2$ was determined on a motor-driven treadmill. The treadmill exercise protocol consisted of a warm-up at a horizontal running speed that elicited a heart rate of approximately 150 beats · min^{-1}. An incremental work load was then performed until voluntary exhaustion. The cross-country skiers also performed an incremental work load test that consisted of roller-skiing or roller-blading on the treadmill until voluntary exhaustion. The cyclists performed $\dot{V}O_2max$ tests on both the Monark cycle ergometer and the Schwinn Airdyne ergometer. These tests consisted of incremental work load to voluntary exhaustion. When 2 tests were performed, the highest obtained $\dot{V}O_2max$ value was used in the data analysis. These test protocols were designed to test the athlete in her specific sport, which has been shown to elicit the most accurate $\dot{V}O_2max$ values.[19-21]

During each $\dot{V}O_2max$ test, heart rate was recorded each 5 seconds by telemetry with a Quantum XL heart rate monitor. A printout of the heart rate was obtained at the end of each exercise bout via a Commodore computer. Open circuit spirometry was used to determine oxygen uptake. Inspired air was measured for ventilation by a Parkinson-Cowan gasmeter. Expired mixed air gas fractions were analyzed by Ametek O_2 (S-3A1) and carbon dioxide (CD-3A) analyzers. Electrical signals were fed into an Apple II computer via an A/D converter, from which pulmonary ventilation (V_E, liters/min), oxygen uptake ($\dot{V}O_2$, ml/kg/min and liters/min), and carbon dioxide production ($\dot{V}CO_2$, liters/min) were calculated by Rayfield software (Rayfield Equipment, Waitsfield, Vermont). $\dot{V}O_2$ and $\dot{V}CO_2$ were corrected to standard temperature pressure dry (STPD), and a printout of data was obtained every 30 seconds. $\dot{V}O_2max$ was calculated from the 2 highest contiguous 30-second values.

Left ventricular dimensions and mass: LV dimension and mass were assessed in all subjects by magnetic resonance imaging. Prior studies from this institution have found LV mass as determined by magnetic resonance imaging to be highly correlated ($r = 0.98$) to the weight of the left ventricle of Canine[14] and human[15] cadaver hearts. Magnetic resonance imaging was performed using a Diasonics 0.35 tesla magnetic resonance imaging device. This system uses a spin-echo pulse sequence gated by electrocardiogram. A series of 10 images of parallel slices was taken from the cardiac apex to the base. Each slice was obtained at the same point in the cardiac cycle. Images were obtained throughout the cardiac cycle ranging from end-diastole to end-systole. The 5 images obtained at end-diastole and the 5 images obtained at 50 ms after end-diastole were used to calculate LV volume. Images were assessed in a blinded fashion. Intraobserver reproducibility was 0.96.

Software available on the imaging device was used to determine LV wall volume. A trackball was used to outline LV epicardium and endocardium of the 10 images obtained including papillary muscle. If no myocardium was seen this image was not included. The number of voxels (volume elements within the epicardial and endocardial borders) was then calculated. This procedure was repeated 3 times for each of the 10 images, and then the values were averaged. The mean number of voxels representative of myocardium was summed over the entire heart. This number was then multiplied by the volume per voxel to obtain the total volume of myocardium. As determined by phantoms, voxel volume was 1.70 mm × 1.70 mm with an interslice thickness of 10.1 mm. The mass of the left ventricle was then calculated by multiplying the total myocardial volume by the density of myocardial tissue (1.05 g/ml). In addition, calculations were made to determine LV end-diastolic volume and mean wall thickness. LV end-diastolic volume was calculated from the product of the sum of the voxels within the endocardial border and the volume per voxel. Mean wall thickness was calculated from the average thickness of all slices excluding apical and basal slices. Wall thickness for each slice was calculated from the difference of the radii of the area con-

TABLE II Maximal Exercise Values for the Groups

Variable	Long-Distance Runners (n = 13)	Cyclists (n = 12)	Cross-Country Skiers (n = 11)	Sedentary Controls (n = 10)
Heart rate maximum (beats · min^{-1})	187 ± 9	187 ± 9	191 ± 8	193 ± 5
Maximal oxygen uptake (L · min^{-1})	3.40 ± 0.30	3.59 ± 0.32	3.71 ± 0.34	1.91 ± 0.16*
Maximal oxygen uptake (ml · kg^{-1} · min^{-1})	63 ± 5	62 ± 7	62 ± 3	35 ± 4*

*Significantly different from long-distance runners, cyclists and cross-country skiers ($p < 0.05$).
All values are mean ± SD.

TABLE III Group Values for Left Ventricular Mass

Variable	Long-Distance Runners (n = 13)	Cyclists (n = 12)	Cross-Country Skiers (n = 11)	Sedentary Controls (n = 10)
LV mass (g)	154 ± 14	160 ± 24	163 ± 19	115 ± 15*
LV mass/body weight (g · kg^{-1})	2.87 ± 0.33	2.78 ± 0.39	2.74 ± 0.23	2.10 ± 0.38*
LV mass/body surface area (g · kg^{-1} · m^{-1})	96 ± 9	98 ± 14	98 ± 10	72 ± 10*
LV mass/lean body weight (g · kg^{-1})	3.19 ± 0.35	3.22 ± 0.41	3.11 ± 0.28	2.70 ± 0.40*

*Significantly different from long-distance runners, cyclists and cross-country skiers ($p < 0.05$).
All values are mean ± SD.

tained within the endocardium and the area within the epicardium plus endocardium.

Statistical methods: One-way analysis of variance was used to determine significant differences among group means. An α value of 0.05 was accepted as significant. Post-hoc analysis was performed using the student Newman-Keuls procedure. Least-squares linear regression analysis was used to develop correlation coefficients between dependent and independent variables.

RESULTS

Subject characteristics: The endurance athletes and sedentary control subjects were similar ($p > 0.05$) in height, weight and body surface area (Table I). The cross-country skiers were significantly younger than the long distance runners. Percent body fat was similar ($p > 0.05$) among all athletic groups, although cross-country skiers had a greater lean body weight than long distance runners. The sedentary women had a significantly smaller lean body weight and greater percent body fat than the athletes.

Maximal oxygen uptake: $\dot{V}O_2$max was significantly greater for all athletes than for control subjects when expressed in absolute values and when adjusted for body weight (Table II). There were no differences in $\dot{V}O_2$ max among the athletes. Maximal heart rates were similar ($p > 0.05$) for all groups. Absolute $\dot{V}O_2$max was significantly ($p < 0.05$) correlated to lean body weight

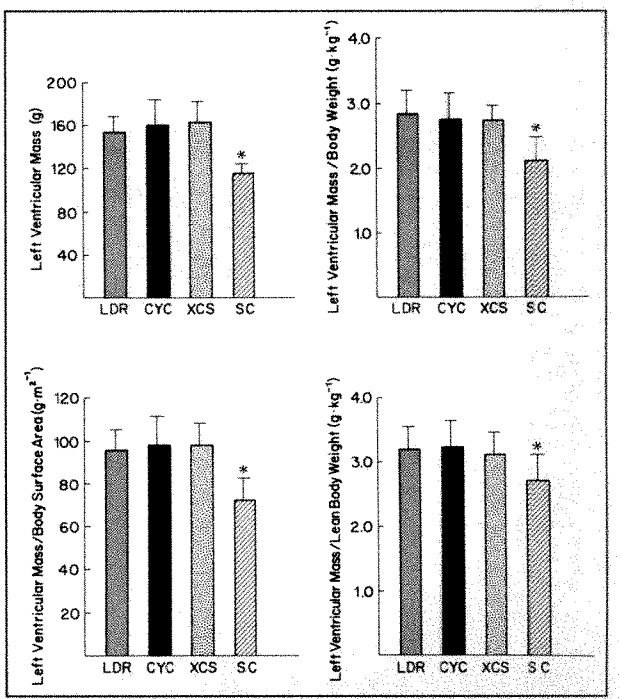


FIGURE 1. Comparison between long-distance runners (LDR), cyclists (CYC), cross-country skiers (XCS) and sedentary control subjects (SC) for absolute left ventricular mass (g) and normalized to body weight, body surface area and lean body weight. *SC significantly different from LDR, CYC and XCS ($p < 0.05$).

TABLE IV Group Values for Left Ventricular End-Diastolic Volume

Variable	Long-Distance Runners (n = 13)	Cyclists (n = 12)	Cross-Country Skiers (n = 11)	Sedentary Controls (n = 10)
LV end-diastolic volume (ml)	114 ± 9	128 ± 19	126 ± 17	93 ± 10*
LV end-diastolic volume/body weight ($ml^3 \cdot kg^{-1}$)	2.12 ± 0.20	2.24 ± 0.39	2.13 ± 0.31	1.68 ± 0.28*
LV end-diastolic volume/body surface area ($ml \cdot m^{2-1}$)	71 ± 6	79 ± 12	77 ± 11	58 ± 7*
LV end-diastolic volume/lean body weight ($ml^3 \cdot kg^{-1}$)	2.36 ± 0.22	2.58 ± 0.38	2.43 ± 0.39	2.17 ± 0.31†

*Significantly different from long-distance runners, cyclists and cross-country skiers ($p < 0.05$).
†Significantly different from cyclists.
All values are mean ± SD.

($r = 0.81$, $p = 0.0001$), body weight ($r = 0.31$, $p = 0.04$) and body surface area ($r = 0.33$, $p = 0.03$).

Left ventricular mass: Absolute LV mass was similar ($p > 0.05$) for all athletes, but significantly greater than that for sedentary control subjects (Table III and Figure 1). When normalized for bodyweight, body surface area and lean body weight, LV mass was still significantly greater in athletes than in control subjects. LV mass was moderately correlated with lean body weight ($r = 0.67$, $p = 0.0001$) (Figure 2) and $\dot{V}O_2$ ($r = 0.79$, $p = 0.0001$) (Figure 3), respectively, and demonstrated a low correlation with body weight ($r = 0.31$, $p = 0.04$) and body surface area ($r = 0.32$, $p = 0.03$).

Left ventricular end-diastolic volume: LV end-diastolic volume was similar among all endurance trained groups and was significantly larger than in the sedentary control subject (Table IV and Figure 4). The ratio of LV end-diastolic volume/body weight and LV end-diastolic volume/body surface area revealed significantly larger ratios for all athletic groups than for sedentary control. LV end-diastolic volume/lean body weight ratio was similar among all athletic groups. However, only cyclists had larger LV end-diastolic volume/lean body weight ratios than sedentary control subject. End-diastolic volume was significantly related to lean body weight ($r = 0.50$) (Figure 5) and to $\dot{V}O_2$ ($r = 0.71$) (Figure 6), but not to body weight ($r = 0.22$, $p = 0.15$) or to body surface area ($r = 0.18$, $p = 0.23$).

Left ventricular mass to end-diastolic volume ratio and mean wall thickness: LV mass/LV end-diastolic volume ratio was similar for all groups (mean 1.30 ±

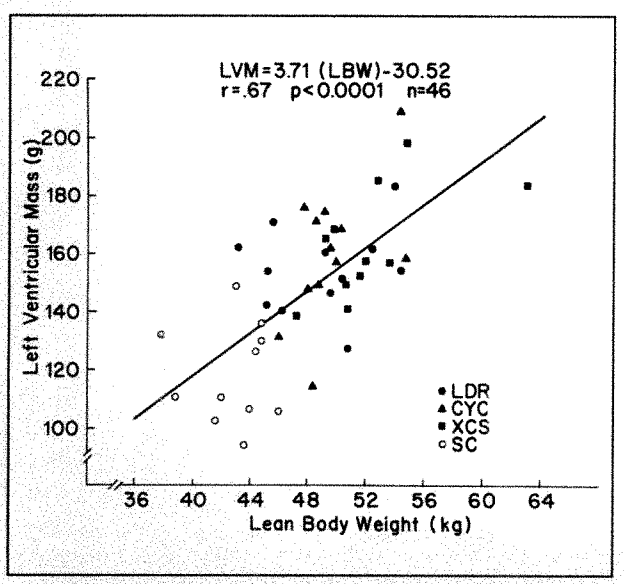


FIGURE 2. Left ventricular mass (LVM) (g) in relation to lean body weight (LBW) (kg) for all endurance athletes and control subjects. Other abbreviations as in Figure 1.

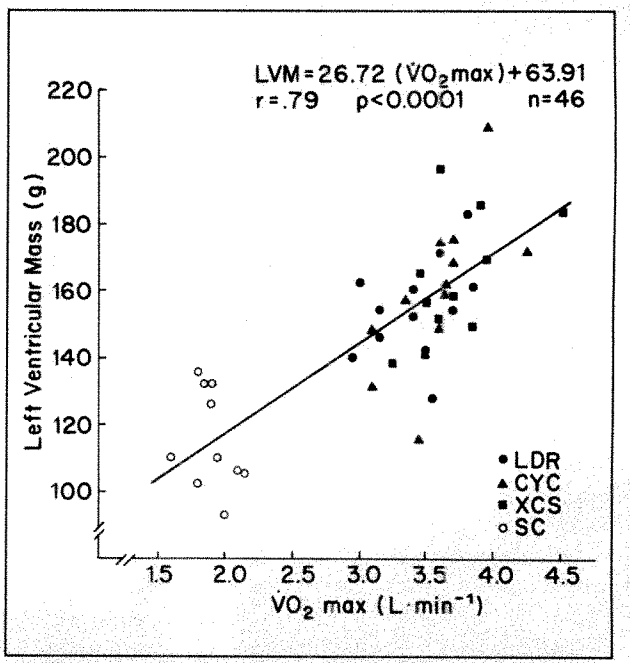


FIGURE 3. Left ventricular mass (LVM) (g) in relation to maximal oxygen uptake ($\dot{V}O_2$ max) ($L \cdot min^{-1}$) for endurance athletes and control subjects. Other abbreviations as in Figure 1.

0.16) (Figure 7). Mean wall thickness was similar for all endurance groups (mean 11.5 ± 1.29 mm) (Figure 7) and significantly greater than that for sedentary control subjects (mean 9.8 ± 0.9 mm). Mean wall thickness was significantly correlated with lean body weight ($r = 0.59$, $p = 0.0001$) and with absolute $\dot{V}O_2$ ($r = 0.56$, $p = 0.0002$).

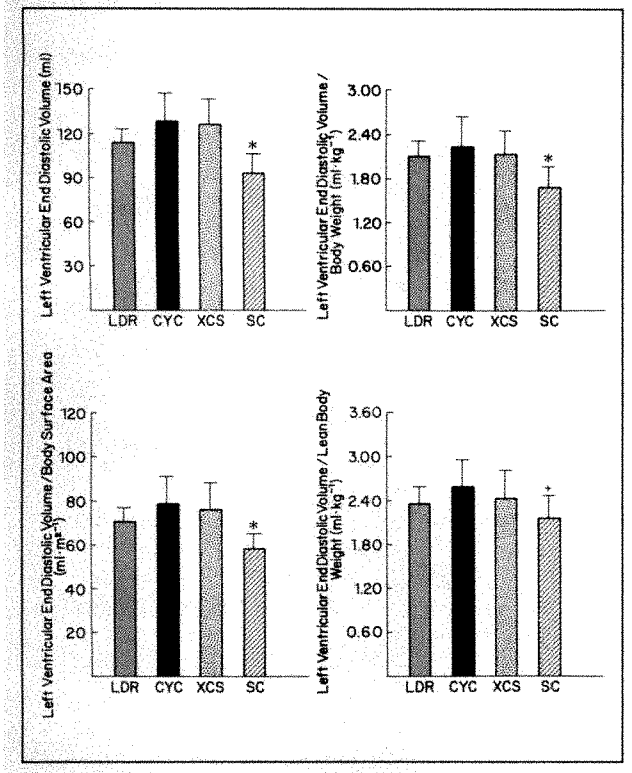


FIGURE 4. Comparison between long-distance runners (LDR), cyclists (CYC), cross-country skiers (XCS) and sedentary controls (SC) for absolute left ventricular end-diastolic volume (ml) and normalized to body weight, body surface area and lean body weight. *SC significantly different from LDR, CYC and XCS ($p < 0.05$). +SC significantly different from CYC ($p < 0.05$).

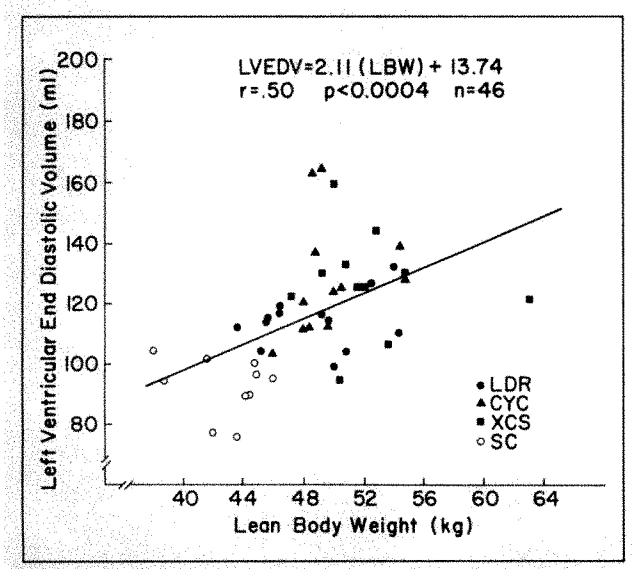


FIGURE 5. Left ventricular end-diastolic volume (LVEDV) (ml) in relation to lean body weight (kg) for endurance athletes and control subjects. Other abbreviations as in Figures 1 and 2.

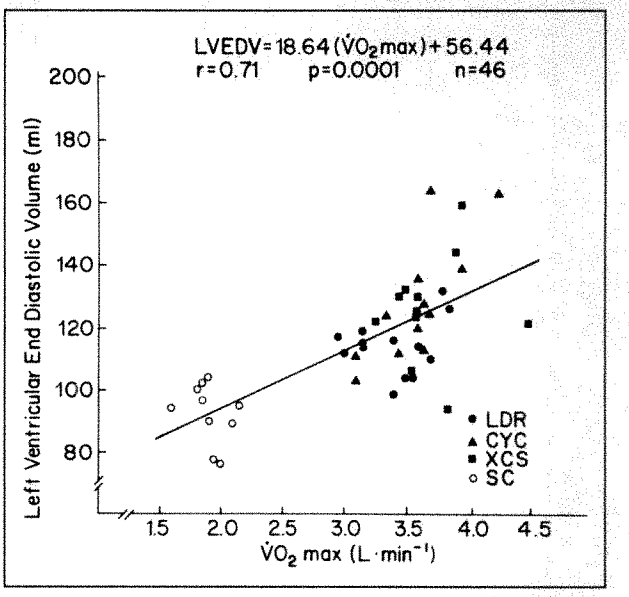


FIGURE 6. Left ventricular end-diastolic volume (LVEDV) (ml) in relation to maximal oxygen uptake ($\dot{V}O_2$ max) ($L \cdot min^{-1}$) for endurance athletes and control subjects. Other abbreviations as in Figure 1.

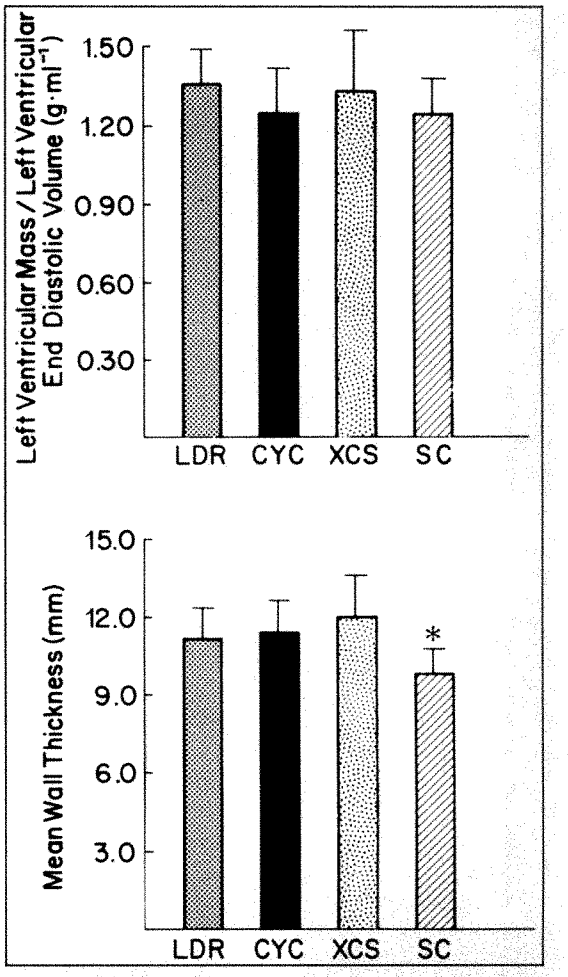


FIGURE 7. Comparison between long-distance runners (LDR), cyclists (CYC), cross-country skiers (XCS) and sedentary controls (SC) for absolute left ventricular mass to left ventricular end-diastolic volume ratio ($g \cdot ml^{-1}$) and mean wall thickness (mm). *SC significantly different from LDR, CYC and XCS ($p < 0.05$).

TABLE V Studies of Left Ventricular Mass in Female Athletes

Study	Subjects	No.	$\dot{V}O_2$max	Wall Thickness	LVEDV	LVM	% Diff.	LVM/m^2	LVM/LVEDV
Cohen (1980)	Dancer	15	—	10.3*	81	189	34	123	—
	Controls	7	—	8.8*	69	141		95	—
Mickelson (1986)	Runners	32	—	11.0	99	142	38	89	1.43
	Controls	40	—	6.6	85	103		64	1.21
Mumford (1981)	Runners	9	—	10.5†	93	205	45	130	—
	Controls	9	—	8.6†	83	142		86	—
Rubal (1981)	Softball players	9	55	8.5*	110	168	37	—	—
	Controls	10	40	7.4*	88	123		—	—
Rubal (1987)	Dancers	8	52	7.2*	110	143	14	86	—
	Runners	6	59	7.6*	130	164	30	110	—
	Swimmers	10	56	7.9*	108	153	21	93	—
	Sprinters	8	58	8.0*	115	163	29	99	—
	Basketball players	9	N/M	7.7*	149	180	43	98	—
	Controls	30	40	7.3*	96	126		77	—
Zeldis (1978)	Hockey players	—	52	9.5*	108	178	39	110	—
	Controls	—	41	9.5*	77	128		82	—

*Average of intraventricular septal wall thickness and left posterior wall thickness.
†Left ventricular posterior wall thickness.
Values represent mean ± SD.
Diff. = difference; LVEDV = left ventricular end-diastolic volume; LVM = left ventricular mass; $\dot{V}O_2$max = maximal oxygen uptake.

DISCUSSION

The effect of endurance training on heart size has been investigated for many years. Early studies using physical diagnosis, roentgenography, electrocardiography and autopsy studies have suggested increased heart size in athletes.[22,23] More recently LV mass has been examined by echocardiography, and numerous studies[1,2,4,6,22] have noted an increase in LV mass of male athletes.

Most of the studies that have addressed the question of the effect of exercise on LV mass in female athletes[7–12] have reported that LV mass is increased. However, most of these studies have used M-mode echocardiography to determine LV mass. They have been limited by the following: (1) lack of measurements of cardiovascular functional capacity, such as $\dot{V}O_2$max; (2) absence of anthropometric and body composition measurements for purposes of normalizing cardiac measures; and (3) failure to determine interrelationships between LV mass and physical characteristics such as body weight, body surface area and lean body weight. These conditions are necessary for determining accurate LV mass, establishing endurance capacities of the subjects, and examining which factors are contributing to increased LV mass.

Some investigators[3,6,13] have questioned whether M-mode echocardiography is able to precisely measure LV wall and chamber dimensions because of the formulas that require the cubing or squaring of 1-dimensional data for the calculation of LV mass.[3,6,24] In addition, assumptions of LV geometry, usually assuming that the ventricle is an ellipsoid, are necessary in these formulas and may lead to further inaccuracies in LV mass calculations.[12]

An increase in LV chamber size with a concomitant increase in LV mass has been described as eccentric hypertrophy, whereas an increase in LV mass without a change in chamber size is defined as concentric hypertrophy. It has been hypothesized that endurance training leads to increased LV end-diastolic volume secondary to a chronic volume overload, and that endurance training leads to an increase in LV mass because of an increase in systolic blood pressure during exercise. Other investigators suggest that the increase in mass is a consequence of the increase in LV end-diastolic volume in accordance with the law of La Place, which states that wall stress is equal to (pressure × radius)/wall thickness: $\sigma = (P \cdot r)/w$. Thus, volume overload would increase wall stress (i.e., increase LV end-diastolic volume) and therefore an appropriate increase in wall thickness would occur to relieve this stress.

Left ventricular mass: Most cross-sectional echocardiographic studies of female athletes have found increased absolute mass compared with sedentary control subjects (Table V). Cohen[7] Mickelson,[8] Rubal[10] and Zeldis[12] and their co-workers found that female athletes had significantly larger absolute masses than did control groups, similar to our current study. Rubal et al,[11] in studying several different groups of athletes, found that only long distance runners and basketball players had significantly larger LV masses than did control subjects.

Only a few studies of female athletes have simultaneously measured $\dot{V}O_2$max and heart mass. Rubal[10,11] and Zeldis[12] and their associates (Table V) reported larger $\dot{V}O_2$max values for female athletes than for control subjects, similar to results in the present study (Table II). These results confirm prior findings that athletes have a higher level of endurance training and higher $\dot{V}O_2$max than do sedentary women.

It is well documented that endurance-trained athletes have a greater $\dot{V}O_2$max than do sedentary people. Many studies also have suggested that endurance ath-

letes have larger hearts or larger LV masses, or both. However, to our knowledge only 1 other study has directly examined the relationship between $\dot{V}O_2$max and LV mass in women. Rubal et al[11] found a significant relationship between $\dot{V}O_2$max and LV mass ($r = 0.323$, $p < 0.05$) among all subjects. In an investigation of men, Milliken et al[16] found that LV mass measured by magnetic resonance imaging was significantly correlated with $\dot{V}O_2$max ($r = 0.80$). In the present study, $\dot{V}O_2$ max was significantly related to LV mass ($r = 0.79$). Our elite, female endurance athletes had an overall mean $\dot{V}O_2$max of 62 ml · kg^{-1} · min^{-1}, indicating a very high level of cardiovascular fitness. Furthermore, these athletes — long-distance runners, cyclists and cross-country skiers — had been competing in their sports for 7, 3 and 9 years, respectively. Thus, our findings confirm that endurance training, or at least the capacity to do extensive endurance training, is a significant factor in the development of a larger LV mass in female athletes than in sedentary women.

Left ventricular end-diastolic volume: In the present study, LV end-diastolic volume was similar in all athletic groups and larger than that in sedentary control subjects. Cohen,[7] Mickelson,[8] Rubal[10] and Zeldis[12] and their co-workers also found significantly larger LV end-diastolic volume for their athletic groups than control subjects (Table V). In addition, Rubal et al[11] found that among several athletic groups only long distance runners and basketball players had larger LV end-diastolic volumes than controls. Our values for LV end-diastolic volume were somewhat larger than those reported in other studies; however, our values fall within the normal limits of LV end-diastolic volume for body surface area as reported by Valdez et al.[25] In the present study, LV end-diastolic volume/body surface area and LV end-diastolic volume/body weight ratios were similar among the athletic groups and larger than those of sedentary women. Mumford and Prakash[9] reported larger LV end-diastolic volume/body surface area ratios for runners than for control subjects, whereas Cohen et al[7] found no difference in LV end-diastolic volume/body surface area ratios between dancers and control subjects. Rubal et al[11] found that only long-distance runners and basketball players had larger LV end-diastolic volume/body surface area ratios than control subjects, whereas his other athletic groups did not. LV end-diastolic volume was significantly correlated with lean body weight ($r = 0.53$) and $\dot{V}O_2$max ($r = 0.71$) in this study. Zeldis et al[12] found that LV end-diastolic volume/body surface area was significantly correlated with $\dot{V}O_2$max ml · kg^{-1} · min^{-1} ($r = 0.63$).

Left ventricular mass/volume ratio and mean wall thickness: Mean wall thickness was observed in the present study to be larger in the endurance athletes than in sedentary control subjects. Some prior studies of female athletes have reported increases in LV posterior wall thickness[7,20] compared with sedentary control subjects. Other studies have found no differences in intraventricular septal thickness[11,12] or in LV posterior wall thickness,[10–12] whereas Mickelson[8] found no difference in LV wall thickness between runners and control subjects. Our wall thickness was calculated from the mean of numerous measurements taken through the heart, as opposed to echocardiographic studies in which only 1 measurement is obtained. This suggests that the finding of no difference in wall thickness between athletes and control subjects in previous studies may be due to the limitations of echocardiography, or to studying subjects who are not as well trained as our endurance athletes.

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5 mg 10 mg

PLENDIL focuses more activity on vascular smooth muscle than cardiac muscle, reducing blood pressure principally as a consequence of a dose-related decrease of peripheral vascular resistance in man with a modest reflex increase in heart rate.

CONTRAINDICATIONS: PLENDIL is contraindicated in patients who are hypersensitive to this product.

PRECAUTIONS: General: ***Hypotension:*** Felodipine, like other calcium antagonists, may occasionally precipitate significant hypotension and rarely syncope. It may lead to reflex tachycardia which in susceptible individuals may precipitate angina pectoris. (See ADVERSE REACTIONS.)

Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients: Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Beta-Blocking Agents:*** A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively. In controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism*.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year carcinogenicity study in rats fed felodipine at doses of 7.7, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28* times the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy: ***Pregnancy Category C:*** *Teratogenic Effects:* Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers: It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended-release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine, MSD) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (Incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL % N = 730	Placebo % N = 283
Peripheral Edema	22.3 (4.2)	3.5
Headache	18.6 (2.1)	10.6
Flushing	6.4 (1.0)	1.1
Dizziness	5.8 (0.8)	3.2
Upper Respiratory Infection	5.5 (0.1)	1.1
Asthenia	4.7 (0.1)	2.8
Cough	2.9 (0.0)	0.4
Paresthesia	2.5 (0.1)	1.8
Dyspepsia	2.3 (0.0)	1.4
Chest Pain	2.1 (0.1)	1.4
Nausea	1.9 (0.8)	1.1
Muscle Cramps	1.9 (0.0)	1.1
Palpitation	1.8 (0.5)	2.5
Abdominal Pain	1.8 (0.3)	1.1
Constipation	1.6 (0.1)	1.1
Diarrhea	1.6 (0.1)	1.1
Pharyngitis	1.6 (0.0)	0.4
Rhinorrhea	1.6 (0.0)	0.0
Back Pain	1.6 (0.0)	1.1
Rash	1.5 (0.1)	1.1

*Based on patient weight of 50 kg

In the two dose response studies using PLENDIL® (Felodipine, MSD) as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related:

Adverse Effect	Placebo N = 121	5.0 mg N = 72	10.0 mg N = 123	20 mg N = 50
Peripheral Edema	2.5	13.9	19.5	36.0
Palpitation	0.8	0.0	2.4	12.0
Headache	12.4	11.1	18.7	28.0
Flushing	0.0	2.8	8.1	20.0

In addition, adverse experiences that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical studies (listed in order of decreasing severity within each category) and serious adverse events that occurred at a lower rate or were found during marketing experience (those lower rate events are in italics) were: *Body as a Whole:* Facial edema, warm sensation, *Cardiovascular:* Tachycardia, *myocardial infarction, hypotension, syncope, angina pectoris,* arrhythmia; *Digestive:* Vomiting, dry mouth, flatulence; *Hematologic: Anemia; Musculoskeletal:* Arthralgia, arm pain, knee pain, leg pain, foot pain, hip pain, myalgia; *Nervous/Psychiatric:* Depression, anxiety disorders, insomnia, irritability, nervousness, somnolence; *Respiratory:* Bronchitis, influenza, sinusitis, dyspnea, epistaxis, respiratory infection, sneezing; *Skin:* Contusion, erythema, urticaria; *Urogenital:* Decreased libido, impotence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also been studied as monotherapy in 680 patients with hypertension in U.S. and overseas controlled clinical studies. Other adverse experiences not listed above and with an incidence of 0.5 percent or greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointestinal pain; *Musculoskeletal:* Arthritis, local weakness, neck pain, shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respiratory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurred vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in < 0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients.*)

Clinical Laboratory Test Findings: ***Serum Electrolytes:*** No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, *Renal, Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE: Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended initial dose is 5 mg once a day. Therapy should be adjusted individually according to patient response, generally at intervals of not less than two weeks. The usual dosage range is 5-10 mg once daily. The maximum recommended daily dose is 20 mg once a day. That dose in clinical trials showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function, because they may develop higher plasma concentrations of felodipine, should have their blood pressure monitored closely during dosage adjustment (see PRECAUTIONS). In general, doses above 10 mg should not be considered in these patients.

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Diagnosis and Management (by Subxiphoid Pericardiotomy) of Large Pericardial Effusions Causing Cardiac Tamponade

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To determine the clinical features, course and outcome of patients with cardiac tamponade, 57 consecutive patients with new, large pericardial effusions were prospectively studied. Twenty-five patients (44%) developed cardiac tamponade with venous hypertension and a pulsus paradoxus >10 mm Hg. Electrocardiography, radiographic studies and echocardiography did not differentiate patients with and without tamponade. All 57 patients underwent thorough diagnostic evaluation followed by subxiphoid pericardial biopsy and drainage. A diagnosis was obtained in 53 patients (93%). Collagen vascular disease was significantly more frequent in the 25 patients with than in the 32 without cardiac tamponade (24 vs 3%; p <0.05). The frequency of malignant and uremic effusions was equal in both groups, whereas radiation-induced effusions seldom produced tamponade. At 1-year follow-up, 3 patients (12%) with tamponade had recurrent effusions, and 1 needed reoperation. This was not significantly different from the 32 patients without tamponade. Twelve-month mortality was also similar in both groups (36 vs 44%). This prospective series disclosed several unexpected findings: (1) Cardiac tamponade occurred in almost 50% of patients with new large pericardial effusions; (2) both malignancy and collagen vascular disease occurred with equal frequency as etiologies, whereas radiation-induced tamponade was unusual; (3) thorough clinical evaluation resulted in few idiopathic etiologies; and (4) subxiphoid pericardiotomy was effective for both diagnosis and therapy of tamponade.

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Cardiac tamponade can occur from a number of disease processes. As a result, the clinical presentation can vary from a slowly evolving one to a rapidly progressive emergency. Although much has been written about the pathophysiology, physical signs and echocardiographic findings of tamponade, there has not been a large prospective evaluation of its clinical features, course or outcome. This study reports the results of a prospective, nonrandomized trial of subxiphoid pericardiotomy for patients with large pericardial effusions and cardiac tamponade.

METHODS

Patient selection: All echocardiograms of patients admitted to Duke University Medical Center and the Durham Veterans Administration Medical Center from May 1987 through December 1988 were screened. Only patients with large pericardial effusions were selected. Large pericardial effusions were defined as those with both anterior and posterior fluids, and one half centimeter of fluid either anteriorly or posteriorly during diastole. Cardiac tamponade was defined as a pericardial effusion with associated venous hypertension and a pulsus paradox >10 mm Hg.

Seventy-five patients were evaluated, and 57 were enrolled in the study. Eighteen patients were excluded from the protocol for the following reasons: patient refused procedure (n = 7), physician refused procedure (n = 6), chronic stable effusion (>6 months) (n = 3), and patient expired before procedure (n = 2).

Clinical assessment: Each patient was evaluated by 1 of the authors, and a physical examination, and laboratory and radiologic work-up were performed, including a complete blood count, coagulation studies, serum electrolytes and creatinine, blood urea nitrogen, calcium, albumin, protein, liver function studies, lactate dehydrogenase, thyroid studies, antinuclear antibody, rheumatoid factor, tuberculin and control skin tests, appropriate cultures, chest x-ray and electrocardiogram. Acute and convalescent viral serologies for herpes simplex, lymphocytic choriomeningitis virus, cytomegalovirus, influenza and Coxsackie B[1–6] were collected. Other serologies included toxoplasma, legionella, mycoplasma, syphilis and leptospira. Electrocardiographic, echocardiographic and radiographic analyses were performed in an independent, blinded manner.

Intervention: A subxiphoid pericardial biopsy and drainage were performed according to the methods of Fontenelle et al.[1] Pericardial fluid was analyzed for glu-

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TABLE I Symptoms

	Tamponade	Non-tamponade
Dyspnea on exertion	80% (20/25)	72% (23/32)
Dyspnea at rest	64% (16/25)	59% (19/32)
Orthopnea	56% (14/25)	34% (11/32)
Cough	48% (12/25)	41% (13/32)
Chest pain	40% (10/25)	66% (21/32)
Fever	40% (10/25)	31% (10/32)
Edema	32% (8/25)	50% (16/32)
Paroxysmal nocturnal dyspnea	32% (8/25)	19% (6/32)
Abdominal swelling	24% (6/25)	22% (7/32)
Night sweats	16% (4/25)	19% (6/32)
Syncope	8% (2/25)	0% (0/32)
None	0% (0/25)	3% (2/32)

TABLE II Signs

	Tamponade	Non-tamponade
Temperature (C°)*	37.2 ± 0.2	37 ± 0.1
Pulse (beats/min)	104 ± 5†	92 ± 3
Respiratory rate	24 ± 1†	20 ± 1
Jugular venous distention (cm H_2O)	14 ± 2‡	8 ± 1
Paradoxical pulse (mean)	18 ± 1‡	5 ± 1
Systolic blood pressure (mm Hg)	124 ± 3	130 ± 5
Diastolic blood pressure (mm Hg)	75 ± 4	80 ± 3
Rales	56% (14/25)	34% (11/32)
Edema	52% (13/25)	38% (12/32)
Friction rub	40% (10/25)†	12% (4/32)
Soft S_1/S_2	28% (7/25)	12% (4/32)
Hepatomegaly	24% (6/25)	12% (4/32)
Kussmaul's	16% (4/25)	19% (6/32)
Ascites	16% (4/25)	12% (4/32)
Ewart's	12% (3/25)	19% (6/32)
Murmur	8% (2/25)	25% (8/32)

*Mean ± SEM.
†$p < 0.05$; ‡$p < 0.001$.

TABLE III Electrocardiographic Findings

	Tamponade	Nontamponade
Sinus tachycardia (≥ 100)	44% (11/25)	31% (10/32)
Low voltage	24% (6/25)	31% (10/32)
Diffuse ST depression	24% (6/25)	16% (5/32)
Diffuse ST elevation	20% (5/25)	12% (4/32)
Electrical alternans	12% (3/25)	6% (2/32)
Diffuse T inversion	12% (3/25)	9% (3/32)
PR depression	8% (2/25)	9% (3/32)
Atrial fibrillation	8% (2/25)	3% (1/32)

TABLE IV Chest X-Ray Findings

	Tamponade	Nontamponade
Enlarged cardiac silhouette	68% (17/25)	75% (24/32)
Right pleural effusion	52% (13/25)	28% (9/32)
Water bottle	32% (8/25)	41% (13/32)
Left pleural effusion	32% (8/25)	25% (8/32)
Infiltrate	16% (4/25)	3% (1/32)
Normal	12% (3/25)	6% (2/32)
Fat pad sign	8% (2/25)	12% (4/32)
Congestive heart failure	8% (2/25)	12% (4/32)
Metastases	8% (2/25)	16% (5/32)

TABLE V Etiologies

	Tamponade	Nontamponade
Malignancy	24% (6/25)	22% (7/32)
Collagen/vascular	24% (6/25)*	3% (1/32)
Uremia	16% (4/25)	9% (3/32)
Viral	8% (2/25)	19% (6/32)
Idiopathic	8% (2/25)	6% (2/32)
Radiation	4% (1/25)	22% (7/32)
Tuberculous	4% (1/25)	6% (2/32)
Other	12% (3/25)	16% (5/32)

*$p < 0.01$.

cose, protein, lactate dehydrogenase, white blood count and differential, red blood count, pH, triglycerides, cholesterol, cytology, and cultures for anaerobic and aerobic bacteria, viruses, mycoplasmas, fungi, chlamydia and mycobacteria. Pericardial tissue was studied pathologically and cultured identically to fluid. Patients were followed in the clinic with serial echocardiograms at 1, 3, 6 and 12 months.

Statistical analysis: Percentages were compared by Fisher's exact test. Quantitative data were compared by unpaired 2-tailed Student's *t* test. A value of $p < 0.05$ was considered statistically significant. Numerical results are given as mean ± standard error of the mean.

RESULTS

Twenty-five of the 57 patients who underwent pericardial biopsy were found to be in cardiac tamponade. These patients were compared with the 32 without tamponade who also underwent subxyphoid pericardiotomy. Presenting symptoms are listed in Table I. No significant differences between groups were found. On initial examination, pulse, respiratory rate and presence of a friction rub were statistically higher in the tamponade group (Table II).

Electrocardiographic analysis revealed sinus tachycardia and low voltage as the most frequent findings in both groups (Table III). All electrocardiographic signs were similar between patients with and without tamponade. The most frequent radiographic findings (Table IV) included an enlarged cardiac silhouette, water-bottle heart and pleural effusions. Right pleural effusion was more frequent in the tamponade group (52 vs 28%). The fat pad sign was only seen in 6 patients. Echocardiographic signs of right ventricular diastolic collapse and persistent vena caval phlethora on inspiration did not detect the presence of tamponade.

Subxyphoid pericardiotomy was performed under local anesthesia in 81% of the patients without and in 68% with tamponade. Complications were confined to 2 patients, and consisted of hypotension (tamponade patient) and a postoperative fistula (non-tamponade patient). Etiologies of effusions in both tamponade and non-tamponade patients are listed in Table V. Only 7% (4 of 57) of patients were diagnosed as having idiopathic pericarditis.

Each patient was followed for 12 months. Effusions recurred in 3 patients with tamponade (12%), but only 1 (4%) needed reoperation. Similarly, 4 patients (12%) not in tamponade had recurrent effusions, 3 (9%) of

whom underwent reoperation. Mortalities were similar for both groups (Table VI).

TABLE VI Mortality

	Tamponade	Non-tamponade
Operative	0% (0/25)	0% (0/32)
1 month	12% (3/25)	12% (4/32)
2 months	20% (5/25)	16% (5/32)
6 months	32% (8/25)	38% (12/32)
12 months	36% (9/25)	44% (14/32)

DISCUSSION

There are several important findings of this study. First, almost 50% of patients with new, large pericardial effusions presented with cardiac tamponade. Electrocardiography, radiographic studies and echocardiography offered little in differentiating patients with and without tamponade. Collagen vascular disease appeared to be a more frequent cause of tamponade than previous studies suggested, whereas radiation-induced tamponade continued to be unusual. Careful evaluation resulted in few idiopathic etiologies. Finally, subxiphoid pericardiotomy appeared to be an effective diagnostic and therapeutic procedure.

Although pericardial disease is a common entity, pericardial tamponade is often considered an infrequent presenting feature. Previous studies reported tamponade frequencies of 17 to 35%.[2,3] This series suggests that tamponade can be a frequent finding. These findings are similar to those of Colombo et al[4] who found a 44% incidence.

By definition, patients in this series with tamponade had increased systemic venous pressures and a pulsus paradox >10 mm Hg. However, the higher pulse rate, despite a normal blood pressure, is an important finding. As demonstrated in the canine model, mechanisms such as fluid retention with increased venous pressures, increased inotrophy and chronotrophy, and elevated vascular resistance allow systemic blood pressure to remain stable. Ultimately, however, blood pressure decreases and unconsciousness occurs.[5-7]

As reported by Spodick,[8] electrocardiographic changes in patients with tamponade are not specific. Indeed, the most frequent finding in our patients was sinus tachycardia. Electrical alternans was infrequent in contrast to the 20 to 25% incidence found in previous studies.[9,10] However, patients in this study had large but not massive effusions.

Radiographic findings were similar and hence nonspecific for both patient groups. Likewise, echocardiography offered little help. Right ventricular diastolic collapse (12%), as well as the absence of inferior vena cava collapse (22%), had low sensitivity. This is in contrast to previous studies.[11-16] However, measurement of mitral valve inflow velocity by Doppler echocardiography was not performed. This technique has now become routine. The reduction of mitral valve inflow appears to correlate well with tamponade.[17-18]

Malignancy and uremia have historically been the leading causes of tamponade.[3-4,19-20] Their importance was reconfirmed in the present study. Collagen vascular disease has been an infrequent (0 to 8%) cause in most series.[2-4,19] Twenty-four percent (6 of 25) of tamponade patients in this series had underlying collagen vascular disease. However, the etiologic spectrum of this series may be biased by our case composition. This could also explain why previous studies suggested that radiation-induced cardiac tamponade is a frequent occurrence in some medical centers.[21-22] However, this study supports the findings of other series where radiation-induced tamponade had only a 3 to 4% incidence.[2,19]

This report most importantly demonstrates that a well-designed, prospective study can determine the underlying etiology of most large pericardial effusions. This differs from previous retrospective series that reported an idiopathic rate between 14 and 25%.[2,4,19-20] The only other prospective study reported a 63% idiopathic rate.[3]

Controversy exists regarding the choice between pericardiocentesis and surgery for the management of these patients.[23] Despite the potential advantages of direct visualization of the pericardium, manual exploration and disruption of adhesions, and the ability to obtain tissue to improve diagnostic yield, pericardiotomy has not been consistently used.[2] In this study, only 3 patients (12%) with tamponade developed a recurrent effusion, with 1 (4%) needing reoperation. Complications of surgery were low (with no mortality), and 17 of 25 patients with tamponade had only local anesthesia.

Several limitations of this study should be noted. First, patients with only large pericardial effusions were studied. When designing this study, the authors believed that subxiphoid pericardiotomy could be justified only in patients with large effusions. Second, our etiologic spectrum may have been biased. Finally, the omission of mitral valve Doppler flow studies did not allow us to prospectively evaluate its diagnostic sensitivity or specificity.

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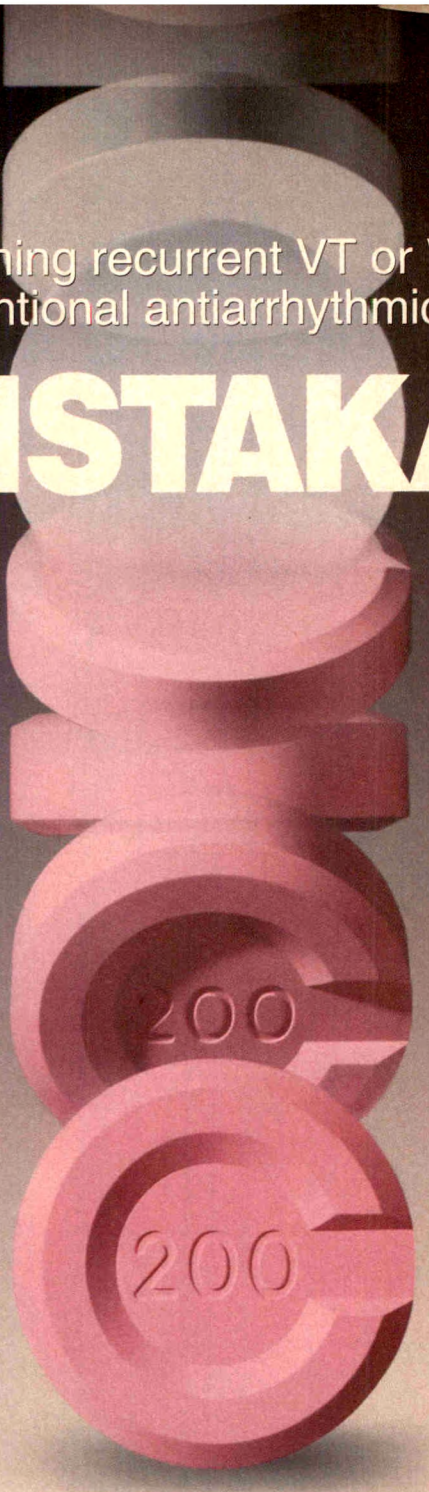
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In life-threatening recurrent VT or VF refractory to conventional antiarrhythmic agents

UNMISTAKABLY



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The most effective antiarrhythmic you can prescribe.

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Cordarone® is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by serious adverse reactions.

See adjacent page for brief summary of prescribing information.

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Cordarone® (amiodarone HCl) Tablets

BRIEF SUMMARY
(See Package Circular for full prescribing information.)

Indications and Usage: Because of life-threatening side effects and substantial management difficulties (See "Warnings" below) use only for treating documented, life-threatening recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia that are unresponsive to documented adequate doses of other antiarrhythmics or when alternative agents are not tolerated.

Controlled trials show no evidence that Cordarone favorably affects survival.

For use only by physicians familiar with and with access to (directly or via referral) all available modalities for treating recurrent life-threatening ventricular arrhythmias, including access to appropriate monitoring facilities and continuous electrocardiographic monitoring and electrophysiologic techniques. Due to the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential arrhythmia exacerbation, start Cordarone in a hospital setting.

Contraindications: Severe sinus-node dysfunction, with marked sinus bradycardia; 2nd- and 3rd-degree atrioventricular (AV) block; episodes of bradycardia which cause syncope (except when used with a pacemaker); known hypersensitivity to the drug.

Warnings: Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/ alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2-5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of Cordarone is an acceptable risk, Cordarone poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using Cordarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Cordarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Cordarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when Cordarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

PULMONARY TOXICITY: Cordarone may cause a syndrome of cough and progressive dyspnea with functional, radiographic, gallium-scan and pathological data consistent with pulmonary toxicity; frequency usually varies from 2-7%, but can be as high as 10-17%. Thus, at start of therapy, perform baseline chest x-ray and pulmonary-function tests, including diffusion capacity. Repeat history, physical exam (PE), and chest x-ray every 3-6 months.

Preexisting pulmonary disease does not appear to increase risk of toxicity; however, prognosis is poorer if pulmonary toxicity develops.

Cordarone-induced pulmonary toxicity seems to result from indirect (hypersensitivity pneumonitis) or direct (interstitial/alveolar pneumonitis) toxicity.

Hypersensitivity pneumonitis usually appears early in therapy; rechallenge results in a more rapid and severe recurrence. Bronchoalveolar lavage is procedure of choice to confirm diagnosis, made when a T suppressor/cytotoxic (CD8 - positive) lymphocytosis noted. Treat with steroids and stop Cordarone.

Interstitial/alveolar pneumonitis, characterized by diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsies. Phospholipidosis (foamy cells, foamy macrophages) is present in most cases of Cordarone-induced pulmonary toxicity; however, this also occurs in approximately 50% of all Cordarone patients. Use these cells as therapy markers, not evidence of toxicity. If interstitial/alveolar pneumonitis is diagnosed, reduce dose or, preferably, withdraw Cordarone, especially if other acceptable antiarrhythmics are available. Where these measures were instituted, symptoms usually decreased in the first week; most clinical improvement was in first 2-3 weeks. Chest X-ray changes usually resolve in 2-4 months. Some experts feel steroids may be helpful. Prednisone (40-60 mg/day) or equivalent doses of other steroids have been used and tapered over several weeks. At times rechallenge at a lower dose will not result in return of toxicity. Reports suggest lower loading and maintenance doses are associated with a lower incidence of pulmonary toxicity.

In Cordarone patients, any new respiratory symptoms suggest a possibility of pulmonary toxicity; repeat and evaluate history, PE, chest X-ray, and pulmonary-function tests (with diffusion capacity). A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as decreases in diffusion capacity approach 30%, sensitivity decreases but specificity increases. A diagnostic gallium scan may also be performed.

Fatalities from pulmonary toxicity occur in about 10% of cases. However, when life-threatening arrhythmias exist, stop Cordarone (amiodarone HCl) cautiously if drug-induced pulmonary toxicity is suspected. As the most common cause of death in these patients is sudden cardiac death, first rule out other causes of respiratory impairment. Bronchoalveolar lavage or lung biopsy may be necessary to confirm the diagnosis, especially when there is no acceptable alternative therapy.

If hypersensitivity pneumonitis is diagnosed, stop Cordarone and treat with steroids. If Cordarone-induced interstitial/alveolar pneumonitis is diagnosed, start steroids and, preferably, stop Cordarone or, minimally, reduce the dose. Some cases may resolve after dose reduction and steroid use. Sometimes, rechallenge at lower doses did not result in return of interstitial/alveolar pneumonitis; however, pulmonary lesions are irreversible in some.

WORSENED ARRHYTHMIA: Cordarone may cause serious exacerbation of a presenting arrhythmia, possibly enhanced by concomitant antiarrhythmic therapy. Exacerbation (about 2-5% in most series), includes new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and Torsade de Pointes. Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients.

LIVER INJURY: Increased hepatic enzymes, mostly asymptomatic, are seen frequently. Consider discontinuation or dose reduction if increase exceeds 3 times normal, or doubles in patient with elevated baseline. Rarely, hepatic failure has been fatal.

PREGNANCY — PREGNANCY CATEGORY D. Cordarone is embryotoxic (increased fetal resorption and growth retardation) in rats at 18 times the maximum recommended oral maintenance dose. Similar results are seen in one mice strain at about 1/2 the maximum recommended maintenance dose or higher, but not in a second strain nor rabbits at doses up to 9 times the maximum recommended maintenance dose.

Neonatal hypo- or hyperthyroidism: In utero exposure can cause fetal harm. There are some reports of congenital goiter/ hypothyroidism and hyperthyroidism. If used anytime during pregnancy apprise patient of potential fetal hazard. In general, use during pregnancy only if potential benefit to the mother justifies unknown fetal risk.

Precautions

CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION: Corneal microdeposits appear in a majority of adults on Cordarone. Usually discernible only by slit-lamp, up to 10% of patients have symptoms like visual halos or blurred vision. Microdeposits are reversible if dose reduced or treatment stopped; if asymptomatic, no need to reduce dose or stop drug.

PHOTOSENSITIVITY: Seen in about 10% of patients; sun-barrier creams or protective clothing may afford some protection. On long-term therapy, may have a blue-gray skin discoloration of exposed skin. Fair complexion or excess sun exposure may increase risk; also may be related to cumulative dose and/therapy duration.

THYROID ABNORMALITIES: Cordarone inhibits conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine, decreased T_3, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. Due to its release of inorganic iodine, or perhaps other reasons, Cordarone can cause either hypo- or hyperthyroidism. Monitor thyroid function before treatment and periodically thereafter, particularly in the elderly and those with history of thyroid nodules, goiter, or other thyroid dysfunction. Due to slow elimination of Cordarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for weeks or months after withdrawal.

Hypothyroidism occurred in 2-4% of patients in most series, but in 8-10% in some. To treat, reduce Cordarone dose and/or give thyroid hormone supplement. Individualize therapy; may need to stop Cordarone.

Hyperthyroidism occurs in about 2% of patients; incidence may be higher with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism is usually a greater hazard than hypothyroidism due to possible arrhythmia breakthrough or aggravation. IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Flat TSH response to TRH is confirmatory. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or Cordarone withdrawal. Antithyroid drugs, β-blockers and/or temporary steroid therapy may be needed. (See full prescribing information for additional information regarding treatment).

SURGERY: ***Hypotension Postbypass:*** Rarely, hypotension is seen on cessation of cardiopulmonary bypass during open-heart surgery in Cordarone patients; relationship to Cordarone is unknown.

Adult Respiratory Distress Syndrome (ARDS): Rarely, ARDS occurs in Cordarone patients after surgery. Patients usually respond to vigorous respiratory therapy; rarely, the outcome is fatal. The mechanism may be generation of superoxide radicals during oxygenation; therefore, keep operative FiO_2 as close to room air as possible.

LABORATORY TESTS: Elevated liver enzymes (SGOT and SGPT) can occur; monitor closely if high maintenance doses used. Consider dose reduction or stopping therapy if significant elevations persist or hepatomegaly occurs.

Thyroid-function tests (increased T_4 and reverse T_3, and decreased T_3) may be altered; despite these changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS: Few drug-drug interactions have been explored formally but most have shown an interaction. Thus, anticipate other interactions, especially drugs with potentially serious toxicity, like other antiarrhythmics. With its long, variable half-life, a potential for interaction also exists with drugs given after stopping Cordarone.

Digitalis: Serum digoxin increases (by up to 70%) and may reach toxic levels; onset is about 1 day. **On initiation of Cordarone, review need for digitalis and reduce its dose by about 50% or stop it.** If digitalis continued, monitor serum levels closely and observe for toxicity. Precautions probably also apply to digitoxin.

Anticoagulants: Potentiation of warfarin-type anticoagulant response is almost always seen and can result in serious or fatal bleeding. Prothrombin time may increase by 100%; onset is 3 to 4 days. **Reduce anticoagulant dose by 1/3 to 1/2, and monitor prothrombin times closely.**

Antiarrhythmic Agents: Although they have been used concurrently with Cordarone, steady-state levels of quinidine, procainamide, and phenytoin may increase during such combined therapy. Quinidine serum concentrations may increase by 33% within 2 days. Procainamide serum concentrations may increase by 55% (n-acetyl procainamide by 33%) in < 7 days. In general, reserve such combinations for patients with life-threatening ventricular arrhythmias incompletely responsive to a single agent, or incompletely responsive to Cordarone (amiodarone HCl), and start any added antiarrhythmic at a lower than usual dose with careful monitoring. During transfer to Cordarone, reduce dose of previous agents 30-50% several days after adding Cordarone; when arrhythmia suppression should be starting. After Cordarone effects are established, discontinue other antiarrhythmics if possible. If treatment is maintained, continue monitoring carefully for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias. In Cordarone patients requiring additional antiarrhythmic therapy, initial dose of such agents should be approximately 1/2 of the usual dose.

Use Cordarone cautiously with β-blockers or calcium antagonists as bradycardia, sinus arrest, and AV block may be potentiated; if necessary, Cordarone can continue after pacemaker insertion in patients with severe bradycardia or sinus arrest.

ELECTROLYTE DISTURBANCES: May be ineffective or arrhythmogenic if hypokalemia is present; correct any potassium or magnesium deficiency before starting drug.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Fertility reduced in male and female rats at 8 x the highest recommended human maintenance dose. Cordarone caused a statistically significant, dose-related increase in thyroid tumors in rats, incidence greater than control even at lowest dose tested, i.e., about 1/2 the highest recommended human maintenance dose. Mutagenicity studies were negative.

PREGNANCY: PREGNANCY CATEGORY D — See **Warnings.**

LABOR AND DELIVERY: Occurrence of adverse effects during labor or delivery is unknown. Preclinical studies in rodents have shown no effect on gestation duration or parturition.

NURSING MOTHERS: Cordarone is excreted in human milk; breast-feeding may expose nursing infants to a significant drug dose. Nursing offspring of lactating rats given Cordarone were less viable and had reduced body-weight gains. Advise mothers to discontinue nursing before taking.

PEDIATRIC USE: Safety and effectiveness have not been established.

Adverse Reactions: Adverse effects are very common (about 3/4 of all patients) with doses of 400 mg/day or more, and cause 7-18% to discontinue. The most serious are pulmonary toxicity, arrhythmia exacerbation, and rare serious liver injury (see "**Warnings**"), but other adverse effects constitute important problems. They are often reversible by reducing dose and virtually always reversible by stopping Cordarone. Most adverse effects appear more frequent with continued treatment beyond 6 months; rates appear relatively constant beyond one year. Neurologic problems, including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy are common (20-40% of patients); these may respond to dose reduction, rarely need to stop therapy.

Gastrointestinal (GI) complaints, commonly seen with high doses (i.e., loading dose), usually respond to dose reduction or divided doses; rarely need to stop drug.

Asymptomatic corneal microdeposits. See **Precautions** and full prescribing information.

Photosensitivity. See **Precautions** and full prescribing information.

Cardiovascular adverse reactions, other than arrhythmia exacerbation, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dose reduction but may require a pacemaker. CHF rarely requires stopping drug. Cardiac conduction abnormalities occur infrequently and are reversible upon stopping drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

Each reported in 10-33% of patients: GI--Nausea and vomiting.

Each reported in 4-9% of patients: Dermatologic--Solar dermatitis/photosensitivity; Neurologic--Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias; GI--Constipation, anorexia; Ophthalmologic--Visual disturbances; Hepatic--Abnormal liver-function tests; Respiratory--Pulmonary inflammation or fibrosis.

Each reported in 1-3% of patients: Thyroid--Hypo- or hyperthyroidism; Neurologic--Decreased libido, insomnia, headache, sleep disturbances; Cardiovascular--CHF, cardiac arrhythmias, SA node dysfunction; GI--Abdominal pain; Hepatic--Nonspecific hepatic disorders. Other--Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

Each reported in < 1% of patients: Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities. Rarely hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia.

Adverse reactions most frequently requiring Cordarone discontinuation include pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, CHF, and elevated liver enzymes. Symptoms causing discontinuation less often include visual disturbances, solar dermatitis, blue skin discoloration, hyper- or hypothyroidism.

Overdosage: The few reports of Cordarone overdose, in which 3 to 8 grams were taken, resulted in no deaths or permanent sequelae. Animal studies indicate that Cordarone has a high oral LD_{50} (>3,000 mg/kg).

Along with general supportive measures, monitor patient's cardiac rhythm and blood pressure; if bradycardia ensues, may use a β-adrenergic agonist or pacemaker. Use positive inotropic and/or vasopressor agents to treat hypotension with inadequate tissue perfusion. Neither Cordarone nor its metabolite is dialyzable.

Dosage and Administration: See full prescribing information.

Manufactured for
Wyeth Laboratories Inc., Philadelphia, PA 19101
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Comparison of Single and Biplane Ventriculography for Determination of Left Ventricular Volume and Ejection Fraction

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This study was done to compare single and biplane left ventriculography in quantitating left ventricular (LV) volumes and ejection fraction. LV volumes and ejection fraction were measured from a 30° right anterior oblique single plane ventriculogram and a 30° right anterior oblique 60° left anterior oblique biplane ventriculogram in 152 men (aged 59 ± 9 [mean ± standard deviation] years), of whom 102 had hypokinesia, akinesia, or dyskinesia. There was excellent agreement between the results of single and biplane ventriculography with respect to LV end-diastolic volume (r = 0.96), end-systolic volume (r = 0.98) and ejection fraction (r = 0.97). The end-diastolic and end-systolic volumes measured by biplane ventriculography were consistently slightly larger than those measured by single plane, whereas ejection fractions measured by the 2 techniques were remarkably similar, even for the 46 patients with biplane ejection fractions <0.50 and the 102 with hypokinesia, akinesia or dyskinesia. Thus, LV volumes and ejection fractions determined by single plane ventriculography correlate very well with those determined by biplane ventriculography, even in patients with hypokinesia, akinesia, or dyskinesia and depressed LV systolic performance. Biplane ventriculography appears to provide little information that cannot be obtained reliably from single plane.

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Cineangiographic left ventriculography may be performed in 1 or 2 planes, depending on the characteristics of the cineangiographic equipment. Single plane ventriculography is typically performed in a 30° right anterior oblique projection; it allows an assessment of (1) the presence and magnitude of asynergy of the anterior, apical and inferior segments; (2) the presence and severity of mitral regurgitation; and (3) left ventricular (LV) volumes and ejection fraction using the area-length method of Dodge et al.[1] Biplane ventriculography is usually performed in 30° right anterior oblique and 60° left anterior oblique projections. In addition to the information provided by single plane ventriculography, biplane ventriculography allows an assessment of the septal, posterior and inferoapical LV segments. Compared with biplane, single plane cineangiographic equipment is less costly to purchase and maintain, easier to operate, and associated with less radiation exposure to the patient and attendant personnel. However, single plane ventriculography does not allow as complete an evaluation of LV regional wall motion. As a result, previous studies[2–5] have emphasized the importance of performing ventriculography in 2 planes to assess LV performance accurately, especially in patients with regional wall motion abnormalities. Although it is assumed that LV volumes and ejection fraction are measured more accurately with biplane than with single plane ventriculography, no previously published report has compared these measurements in a large heterogeneous group of patients, with and without segmental wall motion abnormalities. The present study was performed for this purpose.

METHODS

The cineangiograms of 152 men (aged 59 ± 9 years [mean ± standard deviation], range 32 to 80 years) undergoing catheterization for the evaluation of chest pain were analyzed. In each patient, biplane left ventriculography was performed in 30° right anterior oblique and 60° left anterior oblique projections. From the right anterior oblique projection, anterior, apical and inferior segmental wall motion was assessed, and from the left anterior oblique projection, septal, posterior and inferoapical segmental wall motion was evaluated. For each segment, wall motion was graded as hyperkinetic, normal, hypokinetic, akinetic or dyskinetic. End-diastolic and end-systolic LV silhouettes were traced and digitized via computer (Biomed Data Systems, Arlington, Texas); long axes and areas were determined, and quantitative regional wall motion analysis was performed using 12 radial segments. For each projection, a correction

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factor was generated using the angiographic image of a radioopaque sphere of known diameter. LV volumes were calculated using the area-length method of Dodge et al[1] and corrected using the regression equations of Kennedy et al[6] for single plane and Wynne et al[7] for biplane volumes. Based on quantitative computer analysis, segmental wall motion was graded as normal (regional ejection fraction >0.40 and <0.80), hyperkinetic (regional ejection fraction >0.80), or hypokinetic, akinetic or dyskinetic (regional ejection fraction <0.40). Diffuse hypokinesia was said to be present if all segments in the projection were affected.

All data are reported as mean ± 1 standard deviation. For each variable (end-diastolic volume, end-systolic volume and ejection fraction), the results of the single and biplane calculations were compared with a 2-variable linear regression analysis. For all analyses, a p value <0.05 was considered significant.

TABLE I Clinical and Arteriographic Variables for the 152 Patients

		Hypokinesia, Akinesia, Dyskinesia	
	Total (n = 152)	Absent (n = 50)	Present (n = 102)
No myocardial infarction by history or ECG	69	38	31
Myocardial infarction by history or ECG	83	12	71
Extent of coronary artery disease			
None	24	15	9
1 vessel	36	11	25
2 vessel	38	11	27
3 vessel	39	5	34
Left main	15	8	7

ECG = electrocardiogram.

RESULTS

Of the 152 patients, 83 (55%) had previous myocardial infarction by history or electrocardiography (76 Q wave, 7 non-Q wave) (Table I). By selective coronary arteriography, 24 had chest pain without significant atherosclerotic coronary artery disease (defined as ≥70% luminal diameter narrowing of a major epicardial coronary artery), whereas the other 128 had coronary artery disease of varying severity (Table I). Of the 152 subjects, 102 had at least 1 segment that was hypokinetic, akinetic or dyskinetic: In 85 subjects, they were observed in both the right and left anterior oblique projections; in 10 patients, only in the right anterior oblique projection; and in 7 subjects, only in the left anterior oblique projection. Among the 102 patients with hypokinesia, akinesia or dyskinesia, a total of 210 segments were hypokinetic, 124 were akinetic and 3 were dyskinetic. Forty-four subjects had hyperkinetic segments, 13 of which were adjacent to segments that were hypokinetic, akinetic or dyskinetic.

There was a close correlation between LV end-diastolic volumes (Figure 1), end-systolic volumes (Figure 2), and ejection fractions (Figure 3) measured by single and biplane ventriculography, with r values of 0.96, 0.98 and 0.97, respectively. LV end-diastolic and end-systolic volumes measured by biplane ventriculography were consistently slightly larger than those measured by single plane (Figures 1 and 2). Ejection fractions measured by single and biplane were remarkably similar (Figure 3). Even for the 46 patients with biplane ejection fractions <0.50, the agreement between single and biplane ventriculography was excellent (Figure 3).

An excellent correlation between single and biplane LV end-diastolic volumes (Figure 4A), end-systolic volumes (Figure 4B) and ejection fractions (Figure 4C) was observed in subjects with (1) normal segmental

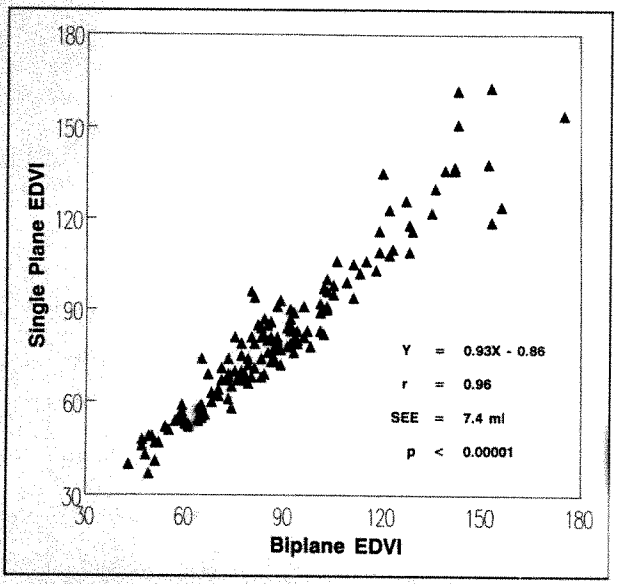


FIGURE 1. A comparison of left ventricular end-diastolic volume index (EDVI), in ml/m², measured from single plane *(vertical axis)* and biplane *(horizontal axis)* ventriculograms. Each symbol represents the data from 1 patient. There was excellent agreement between the results of single and biplane ventriculography. SEE = standard error of estimate.

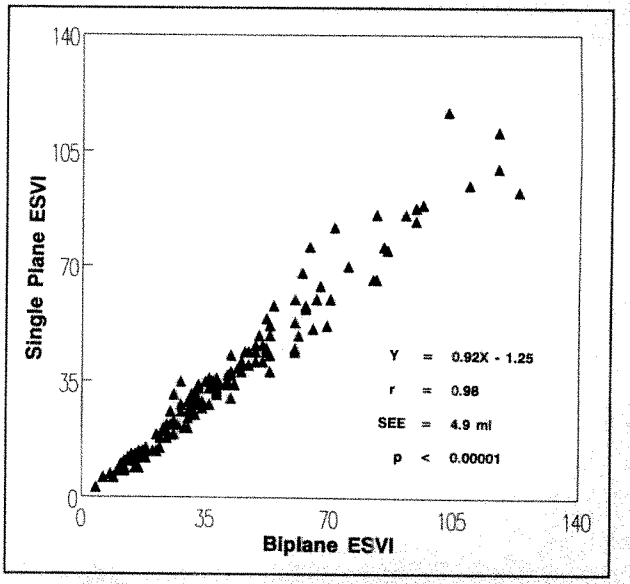


FIGURE 2. A comparison of left ventricular end-systolic volume index (ESVI), in ml/m², measured from single plane *(vertical axis)* and biplane *(horizontal axis)* ventriculograms. Each symbol represents the data from 1 patient. There was excellent agreement between the results of single and biplane ventriculography. SEE = standard error of estimate.

wall motion (n = 19); (2) hyperkinetic segments (n = 45); (3) hypokinetic, akinetic or dyskinetic segments (n = 80); and (4) diffuse hypokinesia (n = 22) by quantitative wall motion analysis. The regression equations comparing single and biplane ventriculography for each of these 4 groups are displayed in Table II.

DISCUSSION

The area-length method of measuring LV volumes from cineangiographic images assumes that the left ventricle is the shape of a prolate ellipse. With biplane ventriculography, the major and both minor axes of the ellipse are measured directly from orthogonal images. If the left ventricle is not distorted in shape, the short axes from both images are similar, so that volumes can be calculated accurately from a single plane image.[8] However, if segmental wall motion abnormalities are present, LV volumes measured from a single plane ventriculogram may be unreliable. Several studies[2-5] have suggested that single plane LV volumes are potentially inaccurate in patients with segmental asynergy, but no report has compared single and biplane volumes and ejection fractions in a large number of patients, many with regional wall motion abnormalities.

Kennedy et al[6] noted that biplane cineangiographic LV volumes were similar to those obtained with single plane cineangiography performed in the right anterior oblique projection and corrected with a regression formula. However, their study has limitations. First, biplane cineangiography was performed in the anteropos-

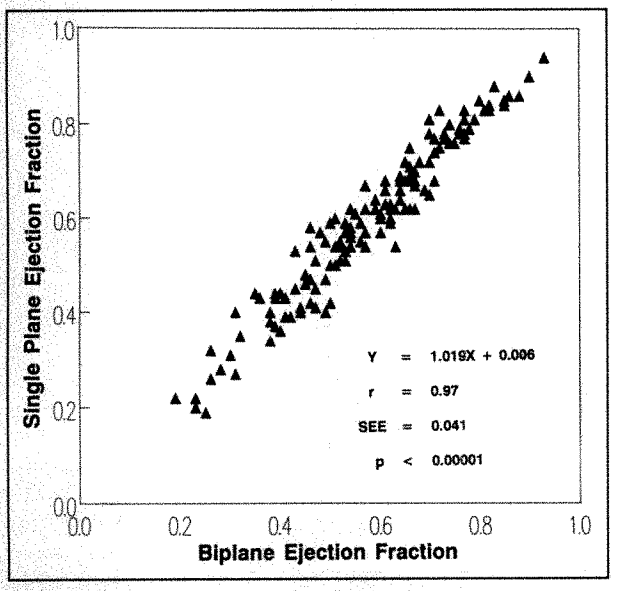
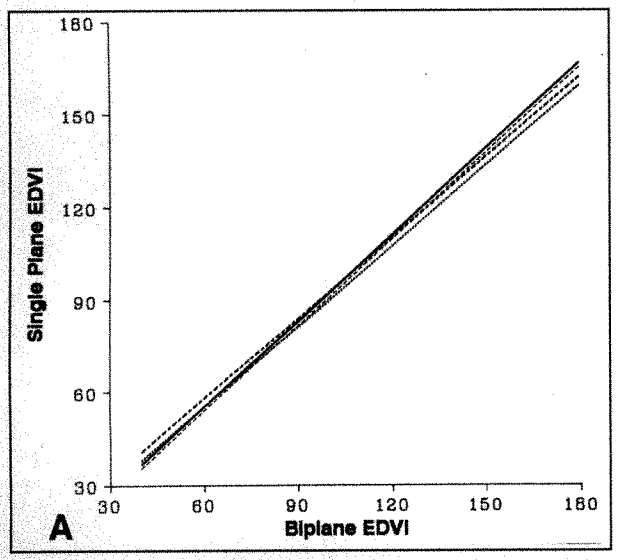


FIGURE 3. A comparison of left ventricular ejection fraction measured from single plane *(vertical axis)* and biplane *(horizontal axis)* ventriculograms. Each symbol represents the data from 1 patient. There was excellent agreement between the results of single and biplane ventriculography. SEE = standard error of estimate.



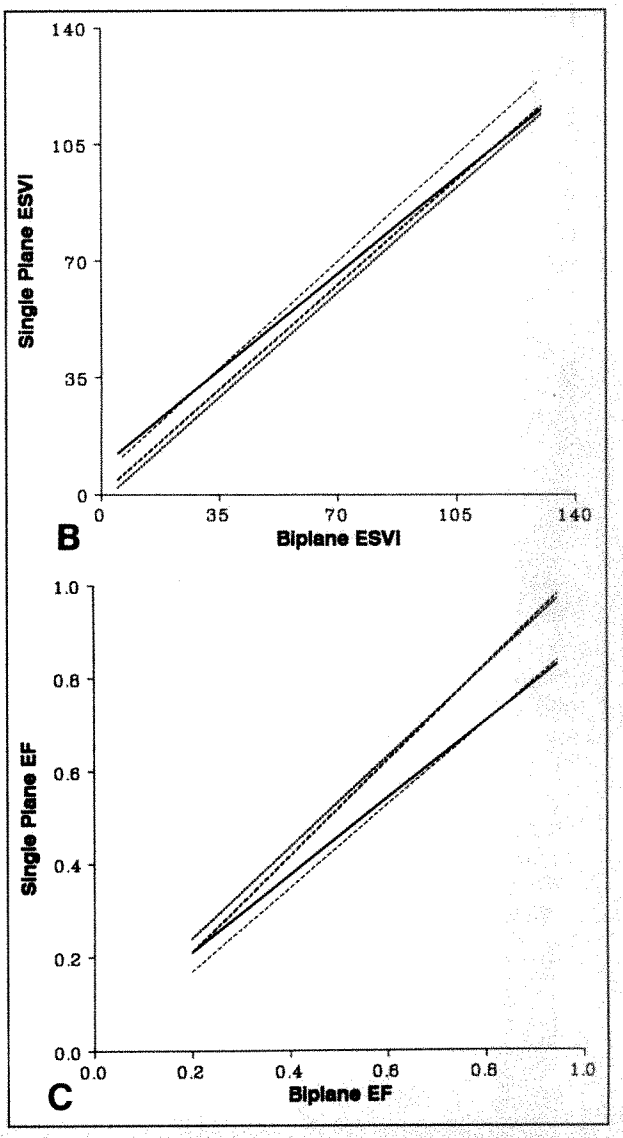


FIGURE 4. A comparison of left ventricular end-diastolic volume index (EDVI), in ml/m² *(A)*, left ventricular end-systolic volume index (ESVI), in ml/m² *(B)*, and left ventricular ejection fraction (EF) *(C)* measured from single plane *(vertical axis)* and biplane *(horizontal axis)* ventriculograms in patients with normal segmental wall motion (n = 19) *(thick dashed lines)*; hyperkinesia of ≥1 segment (n = 45) *(dotted lines)*; hypokinesia, akinesia or dyskinesia of ≥1 segment (n = 80) *(thin dashed lines)*; and diffuse hypokinesia (n = 22) *(solid lines)*. There was excellent agreement between the results of single and biplane ventriculography in each of the 4 groups; furthermore, the groups were similar to one another.

TABLE II Comparison of Single and Biplane Ventriculograms in Patients With and Without Regional Wall Motion Abnormalities

Patient Group	No. of Pts.	Regression Equation	r Value	SEE
Left Ventricular End-Diastolic Volume				
Normokinesia	19	Y = 0.87 X + 5.8	0.88	7.1
Hyperkinesia	45	Y = 0.87 X + 2.9	0.95	4.7
Hypokinesia, akinesia or dyskinesia	80	Y = 0.93 X − 0.9	0.95	6.7
Diffuse hypokinesia	22	Y = 0.93 X − 0.6	0.93	12.6
Left Ventricular End-Systolic Volume				
Normokinesia	19	Y = 0.90 X − 0.1	0.88	3.7
Hyperkinesia	45	Y = 0.90 X − 1.4	0.96	2.1
Hypokinesia, akinesia or dyskinesia	80	Y = 0.92 X + 6.3	0.93	4.2
Diffuse hypokinesia	22	Y = 0.83 X + 8.1	0.94	8.6
Left Ventricular Ejection Fraction				
Normokinesia	19	Y = 1.02 X + 0.01	0.87	0.03
Hyperkinesia	45	Y = 0.97 X + 0.05	0.91	0.04
Hypokinesia, akinesia or dyskinesia	80	Y = 0.89 X − 0.04	0.96	0.04
Diffuse hypokinesia	22	Y = 0.83 X + 0.04	0.87	0.03

SEE = standard error of estimate; X = biplane; Y = single plane.

terior and lateral projections and was filmed at only 6 to 12 frames per second. Currently, most laboratories perform biplane ventriculography in 30° right and 60° left anterior oblique projections, and images are recorded at 30 or 60 frames per second. Second, their data were obtained in only 15 patients, only 2 of whom had depressed LV ejection fractions and none of whom had segmental asynergy. The present study compares LV volumes measured from biplane (30° right and 60° left anterior oblique) and single plane (30° right anterior oblique) projections in 152 patients with and without depressed LV ejection fractions and segmental wall motion abnormalities.

Our data demonstrate an excellent correlation between the single and biplane measurements of LV volumes and ejection fractions. The results of single and biplane quantitation of LV end-diastolic and end-systolic volumes correlated extremely well ($r = 0.96$ and 0.98, respectively), even in patients with segmental asynergy (Figures 1, 2 and 4). Similarly, the results of single and biplane quantitation of LV ejection fraction correlated very well ($r = 0.97$), even in patients with ejection fractions <0.50 (Figure 3) and in those with regional or diffuse wall motion abnormalities (Figure 4C). Thus, when used to measure LV volumes and ejection fraction, biplane ventriculography provides little information that cannot be obtained from single plane.

In this study, LV volumes and ejection fractions obtained from single and biplane left ventriculograms were similar to one another. The volumes obtained from biplane ventriculography were slightly larger than those obtained using single plane. However, since LV volumes were not quantitated by an independent method, we are not certain which technique — single or biplane — provided a more accurate measure of LV volumes. In a previous study from our laboratory,[9] LV volumes and ejection fraction obtained by single plane ventriculography were in close agreement with those determined by radionuclide ventriculography and thermodilution in patients without segmental asynergy. In contrast, in those with segmental wall motion abnormalities, the correlation between the results of angiographic and nonangiographic techniques was poor, presumably because the geometric assumptions on which the area-length method is based were invalid.[9] Because LV volumes calculated from single and biplane ventriculography are in close agreement in these patients, it is likely that biplane ventriculography is no more accurate than single plane for assessing LV volumes in patients with segmental wall motion abnormalities.

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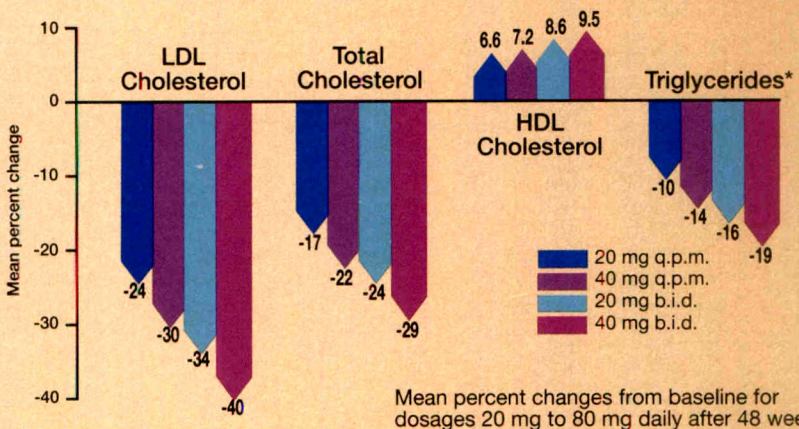
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WARNINGS: *Liver Dysfunction:* Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least 1 year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and, in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated CPK levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 5 patients (0.1%) taking lovastatin alone (1 at 40 mg q.p.m. and 4 at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels >10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy; the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General:* Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in the full Prescribing Information).

Lovastatin may elevate CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin-treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than 2-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Because lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 30 times higher than the mean values in humans taking 80 mg/day. Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on an mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR® [Lovastatin].)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhumurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) the human exposure based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose). MEVACOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking MEVACOR, it should be discontinued, and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences that were rated by the investigator as possibly, probably, or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences: Adverse experiences reported in patients (%) treated with MEVACOR (n=613) in controlled clinical studies are: *Gastrointestinal:* constipation, 4.9; diarrhea, 5.5; dyspepsia, 3.9; flatus, 6.4; abdominal pain/cramps, 5.7; heartburn, 1.6; nausea, 4.7; *Musculoskeletal:* muscle cramps, 1.1; myalgia, 2.4; *Nervous System/Psychiatric:* dizziness, 2.0; headache, 9.3; *Skin:* rash/pruritus, 5.2; *Special Senses:* blurred vision, 1.5; dysgeusia, 0.8.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9%, and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Clinical Adverse Experiences: MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240 to 300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably, or definitely drug related in ≥1% of any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

		MEVACOR			
	Placebo (n=1,663) %	20 mg q.p.m. (n=1,642) %	40 mg q.p.m. (n=1,645) %	20 mg b.i.d. (n=1,646) %	40 mg b.i.d. (n=1,649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably, or definitely drug related in 0.5 to 1% of patients in any drug-treated group are listed below. In all these cases, the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE: After oral administration of MEVACOR to mice, the median lethal dose observed was >15 g/m².

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information for dose-response results).

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically, and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY in the full Prescribing Information and WARNINGS, *Skeletal Muscle*).

For more detailed information, consult your MSD Representative or see the Prescribing Information.

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Marked Benefit with Sustained-Release Niacin Therapy in Patients with "Isolated" Very Low Levels of High-Density Lipoprotein Cholesterol and Coronary Artery Disease

Carl J. Lavie, MD, Lois Mailander, MD, and Richard V. Milani, MD

During the past 2 decades, the cholesterol coronary artery disease (CAD) hypothesis has become established with considerable attention being directed toward lipid intervention for primary and secondary coronary prevention.[1] Although the National Cholesterol Education Program has focused mostly on total cholesterol and low-density lipoprotein (LDL) cholesterol in their assessment and treatment recommendations,[2] recent data from epidemiologic, lipid intervention, coronary angiographic studies, and studies of patients with known severe CAD, suggest that a low level of high-density lipoprotein (HDL) cholesterol is perhaps the strongest lipid risk factor for CAD.[3-6] In fact, a high percentage of patients with CAD have "isolated" low levels of HDL cholesterol.[4] However, nonpharmacologic and drug treatment of patients with isolated low HDL cholesterol has been disappointing.[3,7] Since niacin has beneficial effects on reducing total cholesterol, LDL cholesterol and triglycerides, and also increases HDL cholesterol, it improves the lipid profile in most patients with dyslipidemias. However, the efficacy of niacin therapy in patients with very low levels of HDL cholesterol (e.g., <30 mg/dl), and particularly for isolated low HDL cholesterol, is not established. Therefore, we assessed the efficacy of sustained-release niacin therapy in CAD patients with very low levels of HDL cholesterol, including its effectiveness in a subgroup with isolated low HDL cholesterol compared with a subgroup with hypertriglyceridemia.

We treated 36 consecutive men with known CAD (definite events, angiographic evidence of severe disease, or strongly positive noninvasive tests) and very low levels of HDL cholesterol (<35 mg/dl, and 82% had values <30 mg/dl) with sustained-release niacin (Slo-Niacin®) therapy. None of these patients had major contraindications to niacin therapy, including severe peptic ulcer disease, hepatic dysfunction, diabetes, gouty arthritis, or recent unstable coronary ischemia.[1] A complete lipid profile, including fasting total cholesterol (cholesterol esterase/cholesterol oxidase method), triglycerides (non-free glycerol blanked method), HDL cholesterol (phosphotungstic acid precipitation method), and calculated LDL cholesterol (LDL cholesterol = total cholesterol − HDL cholesterol − triglycerides/5), as well as fasting blood glucose and aspartate transaminase values were obtained at baseline and after 3 months of niacin therapy; repeat aspartate transaminase values were usually assessed after 6 weeks of therapy. Therapy with sustained-release niacin was begun at a dose of 500 mg twice daily with meals, was increased to 3 times daily after 1 to 2 weeks, and then was increased, as tolerated, to 1,000 mg 3 times daily with meals after 4 to 6 weeks of treatment. The average dose used in this 3-month treatment period was 2.4 g/day (range 1,000 to 3,000 mg; median 3,000 mg). All patients had been treated with nonpharmacologic therapy, including exercise and weight reduction, for ≥3 months before instituting niacin therapy. During the time span of this study, patients were instructed to continue with their same program of diet and exercise; none of the patients were treated with other lipid-lowering medications, and other medications known to affect lipids (e.g., β-blockers, diuretics, α-blockers, calcium antagonists) were at stable doses for ≥4 weeks before study entry, and doses were not altered during the program. Niacin therapy was discontinued in 2 patients — for medication intolerance in 1 patient despite a 500 mg/day dose and a >3-fold increase (approximately 1.5 times the upper limit of normal) in the level of aspartate transaminase noted after 6 weeks of therapy (dose 1,500 mg/day) in the other patient who elected not to continue with niacin therapy. Therefore, 34 patients make up the study sample.

Lipid values were compared at baseline and after 3 months of niacin therapy using a paired t test. Subgroup analysis was performed in 19 patients with isolated low HDL cholesterol, defined as LDL cholesterol <160 mg/dl, HDL cholesterol <35 mg/dl, and triglycerides <250 mg/dl, and compared to 10 patients with very low HDL cholesterol and hypertriglyceridemia (>250 mg/dl to <500 mg/dl). Both subgroups were treated with similar doses of niacin. Lipid values in each subgroup were compared at baseline and after drug treatment using a paired t test, and the changes in lipids in the 2 subgroups were compared using a nonpaired t test. Results were expressed as mean ± standard deviation.

Marked improvements in total cholesterol, HDL cholesterol, LDL cholesterol, and LDL/HDL were noted after 3 months of sustained-release niacin therapy (Table I). A slight reduction in triglycerides was noted, but this improvement was not statistically significant. There

TABLE I Lipid Changes with Sustained-Release Niacin in Coronary Patients with Very Low Levels of High-Density Lipoprotein Cholesterol (n = 34)

Lipids	Baseline	3-Month Niacin	% Change	p Value
Total cholesterol (mg/dl)	196 ± 38	174 ± 43	−11	<0.005
Triglycerides (mg/dl)	205 ± 84	201 ± 78	−2	NS
HDL cholesterol (mg/dl)	26 ± 4	33 ± 6	+30	<0.0001
LDL cholesterol (mg/dl)	142 ± 53	114 ± 34	−20	<0.01
LDL/HDL	5.7 ± 2.6	3.6 ± 1.2	−37	<0.0001

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NS = not significant.

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TABLE II Comparison of Niacin Effects in Patients with "Isolated" Low High-Density Lipoprotein Cholesterol Versus Those with Hypertriglyceridemia

	Isolated Low HDL (n = 19)				Hypertriglyceridemia (n = 10)			
Lipid Values	Baseline	3-Month Niacin	% Change	p Value	Baseline	3-Month Niacin	% Change	p Value
Total cholesterol (mg/dl)	189 ± 28	170 ± 42	−10	=0.08	192 ± 46	175 ± 48	−9	NS
Triglycerides (mg/dl)	163 ± 51	180 ± 77	+10	NS	310 ± 47	238 ± 80	−23*	=0.05
HDL cholesterol (mg/dl)	25 ± 4	32 ± 6	+27	<0.002	27 ± 5	38 ± 3	+41	<0.0001
LDL cholesterol (mg/dl)	120 ± 22	114 ± 31	−5	NS	156 ± 80	101 ± 25	−35†	=0.05
LDL/HDL	5.0 ± 1.3	3.7 ± 1.2	−26	<0.01	6.2 ± 4.1	2.7 ± 0.7	−56†	<0.02

*p < 0.05; †p < 0.02 compared with isolated low HDL group.
Abbreviations as in Table I.

TABLE III Lipid Classifications at Baseline and After Three Months of Sustained-Release Niacin Therapy

	Entire Cohort (n = 34)		"Isolated" Low HDL Cholesterol (n = 19)		Hypertriglyceridemia (n = 10)	
Cholesterol (mg/dl)	Baseline (%)	3-Month Niacin (%)	Baseline (%)	3-Month Niacin (%)	Baseline	3-Month Niacin
Total ≥240	6 (18)	4 (12)	1 (5)	2 (11)	2	1
Total <200	23 (68)	26 (76)	14 (74)	15 (79)	7	8
LDL ≥160	9 (27)	4 (12)	0 (0)	1 (5)	3	0
LDL <130	14 (41)	27 (79)	11 (58)	15 (79)	3	10
HDL <35	34 (100)	16 (48)	19 (100)	13 (68)	10	1
HDL <30	28 (82)	9 (26)	17 (89)	7 (37)	7	0

Abbreviations as in Table I.

were no significant changes in body weight, fasting plasma glucose levels, or levels of aspartate transaminase during the time period of the study.

Among the 19 patients with isolated low HDL cholesterol (Table II), significant improvements after niacin therapy were noted in HDL cholesterol and LDL/HDL; however, reductions in total cholesterol ($p = 0.08$) and LDL cholesterol levels were not statistically significant. The level of triglycerides actually increased by 10% in this subgroup of patients, but this increase was also not statistically significant. In the subgroup of 10 patients with both very low HDL cholesterol and hypertriglyceridemia, significant improvements were noted for both HDL cholesterol and LDL/HDL; reductions in both triglycerides and LDL cholesterol levels were of borderline statistical significance ($p = 0.05$). The reduction in total cholesterol in this subgroup did not meet statistical significance. There were no significant changes in body weight, glucose levels or liver function studies in either of these subgroups.

Although the subgroup with isolated low HDL cholesterol had marked improvement in lipids with niacin therapy, the improvements were much more marked in the group with hypertriglyceridemia (Table II), including statistically greater reductions in triglycerides ($p < 0.05$), LDL cholesterol ($p < 0.02$) and LDL/HDL ($p < 0.02$). The increase in HDL cholesterol also appeared greater in the group with hypertriglyceridemia than in those with isolated low HDL cholesterol (+41 vs +27%), but this did not reach statistical significance ($p = 0.14$).

Lipid classifications of these patients are listed in Table III, demonstrating that after therapy with sustained-release niacin, there are striking reductions in the percentage of patients with "high-risk" LDL cholesterol ≥160 mg/dl and low or very low levels of HDL cholesterol, as well as increases in the percentage of patients with "ideal" LDL cholesterol <130 mg/dl. These beneficial improvements in lipid classification were noted in the entire cohort and in the subgroup with isolated low HDL cholesterol, but were more striking in the subgroup with hypertriglyceridemia.

Nearly half of our patients with known CAD and recent major cardiac events have ideal lipids according to the National Cholesterol Education Program, and very few have high-risk lipids (LDL cholesterol ≥160 mg/dl).[4] In unpublished preliminary data from 238 cardiac rehabilitation patients from 2 institutions, approximately one fourth of our patients had isolated low HDL cholesterol, defined as LDL cholesterol <160 mg/dl, HDL cholesterol <35 mg/dl, and triglycerides <250 mg/dl. Isolated low HDL cholesterol was more common than high-risk LDL cholesterol among our cardiac patients, both before and after a program of vigorous nonpharmacologic intervention.

The treatment of patients with low levels of HDL cholesterol has been disappointing, particularly in patients with isolated low HDL cholesterol.[7] In the Helsinki Heart Study, however, drug treatment with gemfibrozil increased HDL cholesterol by an average of 10%; in a subgroup of patients with HDL cholesterol <35 mg/dl, gemfibrozil therapy raised HDL cholesterol by 25%, which was associated with a reduction in CAD-related events by >60%.[8] In the entire trial, for every 1% increase in HDL cholesterol with drug therapy, a >3% reduction in CAD-related events was noted. In trials involving coronary angiography, increases in HDL cholesterol were

related to both reductions in CAD progression, as well as decreased CAD-related events.[9,10]

Only limited data are available, however, on the effects of drug therapy in patients with isolated low HDL cholesterol. In a recent study of 22 patients with isolated low HDL cholesterol using a randomized, crossover design between placebo, lovastatin (20 mg twice daily) and gemfibrozil (600 mg twice daily), modest increases in HDL cholesterol were noted (9% with gemfibrozil and 12% with lovastatin).[7] In this trial, however, there were no significant effects with gemfibrozil on LDL cholesterol or levels of apolipoprotein B, and LDL/HDL was reduced by only 12%; in contrast, these lipid fractions were reduced with lovastatin by 34, 24 and 38%, respectively. It is well known that niacin effectively raises HDL cholesterol, as well as lowers levels of total cholesterol, LDL cholesterol and triglycerides; to our knowledge, however, the efficacy of this therapy in patients with isolated low HDL cholesterol, particularly with very low levels of HDL cholesterol, is not established. Although patients with very low HDL cholesterol and concomitant hypertriglyceridemia seem to benefit more than those with isolated low HDL cholesterol, this report confirms the marked benefit of sustained-release niacin therapy in both groups of patients with low HDL cholesterol, probably greater than that expected with either gemfibrozil or lovastatin.[7]

Several limitations should be noted. First, this was a relatively short treatment study, and the long-term efficacy and adverse effects with sustained-release niacin therapy in these patients are not yet known. Second, the incidence of hepatic toxicity with this sustained-release niacin regimen was quite infrequent in this short-term study. Hepatic dysfunction is known to occur frequently with niacin, much more so with sustained-release preparations.[11] In addition, we have recently reported 3 patients (plus observed 3 unpublished cases) with protein synthesis and clotting factor synthesis deficiency associated with coagulopathy that occurred with sustained-release niacin preparations; this syndrome reoccurred after rechallenge with sustained-release niacin, but not with short-acting niacin preparations.[11] Finally, the sustained-release niacin regimen was extremely well-tolerated in this highly motivated group of patients with CAD who were mainly followed by one clinician (CJL), and these data may not be completely applicable to all patients with CAD or those involved with primary, as opposed to secondary, prevention.

Despite these limitations, the current data support the marked benefits with sustained-release niacin in patients with very low levels of HDL cholesterol, including striking increases in HDL cholesterol and reductions in LDL cholesterol and LDL/HDL, which should prove extremely beneficial for both primary and secondary coronary prevention. Further studies are needed that directly compare niacin with gemfibrozil and hydroxymethylglutaryl coenzyme A reductase inhibitors (e.g., lovastatin, pravastatin and simvastatin), as well as trials combining niacin with either of these classes of agents in various subgroups with low HDL cholesterol. Unlike the combination of lovastatin and gemfibrozil, which is relatively contraindicated because of an approximately 5% risk of rhabdomyolysis, niacin can probably be combined with either of these classes of agents with relatively low risk of serious toxicity.[3]

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Effect of Restenosis After an Earlier Angioplasty at Another Coronary Site on the Frequency of Restenosis After a Subsequent Coronary Angioplasty

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Restenosis remains a major problem in patients undergoing percutaneous transluminal coronary angioplasty. A number of constitutional factors such as male gender,[1] diabetes mellitus,[1,2] cigarette smoking[2] and unstable angina,[1,2] as well as local arterial factors including initial total occlusion,[3] severe residual stenosis[4] and elevated translesional final gradient[1] have been associated with an increased frequency of restenosis. However, these factors are not necessarily causal, and the exact stimulus and mechanism of the cellular response resulting in restenosis remain unknown. In addition, the relative importance of constitutional and local arterial factors on the development of restenosis is unclear. Patients are often referred for angioplasty of atherosclerotic coronary narrowings having previously undergone angioplasty of a different site in the coronary circulation. However, it is not known whether patients in whom restenosis developed after the earlier angioplasty are at increased risk of developing restenosis following angioplasty of a new lesion. The answer to this question could shed some light on the relative contribution of constitutional versus local arterial factors on restenosis. Accordingly, to determine whether restenosis occurs more frequently among patients with a history of restenosis, we performed a retrospective databank analysis of patients at our institution who had undergone angioplasty and identified a select group of patients who had had a successful angioplasty and who subsequently had another angioplasty performed at a different coronary site.

Between October 1, 1979, and March 1, 1990, 3,687 patients underwent coronary angioplasty at our institution. Patients undergoing atherectomy, laser angioplasty and coronary stent placement (n = 231) were excluded. Of the remaining patients, 125 patients were identified as having undergone follow-up angiography ≥2 months after the "initial narrowing" angioplasty, as well as subsequent successful angioplasty of a new narrowing (or narrowings) at a different coronary site (referred to as a "new narrowing" angioplasty). Patients were divided into 2 groups based on the angiographic appearance of the previously dilated initial angioplasty site; patients who had developed restenosis after their initial angioplasty, and those who had not developed restenosis after their initial angioplasty. Five patients underwent coronary artery bypass graft surgery shortly after their second angioplasty without repeat angiography to determine whether restenosis had occurred and were excluded

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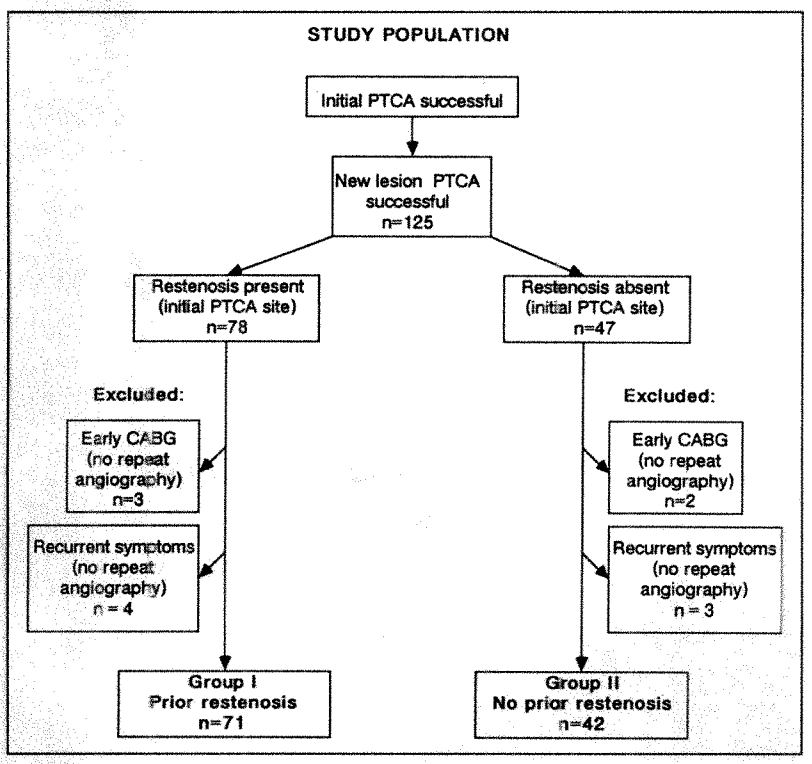


FIGURE 1. Flow diagram representing the formation of the study population after an initial successful coronary angioplasty. All patients subsequently underwent another coronary angioplasty of a new narrowing at a different site in the coronary circulation. CABG = coronary artery bypass grafting; PTCA = percutaneous transluminal coronary angioplasty.

TABLE I Clinical Characteristics Among 113 Patients in the Study Population*

Characteristics	Group I (n = 71)	Group II (n = 42)
Age (years)†	61 ± 12	58 ± 10
Men/women	53 (75%)	30 (71%)
	18 (25%)	12 (29%)
History of diabetes mellitus	11 (15%)	5 (12%)
Current cigarette smoking	13 (18%)	8 (19%)
Hypercholesterolemia (≥250 mg/dl)	35 (49%)	18 (43%)
History of systemic hypertension	31 (44%)	19 (45%)
Prior myocardial infarction	39 (55%)	24 (57%)
Unstable angina pectoris	60 (85%)	33 (79%)

*Patients are grouped according to whether restenosis did (group I) or did not (group II) occur after their first coronary angioplasty.
†Continuous variables expressed as mean ± standard deviation.

TABLE II Angiographic Characteristics of 144 Initial Narrowings Successfully Dilated in the 113 Patients in the Study Population*

Characteristics	Group I (n = 71)	Group II (n = 42)	p Value
Narrowings dilated (no.)	99	50	—
Narrowings dilated per patient	1.39	1.19	—
Left anterior descending artery	48 (48%)	13 (26%)	0.008
Right coronary artery	21 (21%)	19 (38%)	0.029
Left circumflex artery	19 (19%)	17 (34%)	0.026
Vein graft	10 (10%)	1 (2%)	0.074
Left main	1 (1%)	0 (0%)	NS
Pre-PTCA stenosis (%)	88 ± 10	93 ± 7	NS
Total occlusion (no.)	7 (10%)	10 (23%)	
Post-PTCA stenosis (%)	29 ± 12	29 ± 13	NS
Days to restenosis (median)	190	—	—

*Patients are grouped according to whether restenosis did (group I) or did not (group II) occur at these sites.
NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

TABLE III Angiographic Characteristics of 144 New Narrowings Successfully Dilated in 113 Patients to Whom Restenosis had (group I) or Had Not (group II) Occurred After Earlier Angioplasty at a Different Coronary Site

Characteristics	Group I (n = 71)	Group II (n = 42)
Narrowings dilated (no.)	85	57
Narrowings dilated per patient	1.20	1.36
Left anterior descending artery	25 (29%)	22 (39%)
Right coronary artery	27 (32%)	20 (35%)
Left circumflex artery	28 (33%)	15 (26%)
Vein graft	5 (6%)	0 (0%)
Pre-PTCA stenosis (%)	82 ± 11	87 ± 11
Post-PTCA stenosis (%)	28 ± 11	29 ± 10
Initially totally occluded	3 (4%)	4 (10%)
Multivessel disease	50 (70%)	30 (71%)
Days between initial and new narrowing PTCA (median)	223	650

PTCA = percutaneous transluminal coronary angioplasty.

from analysis (3 with initial narrowing restenosis and 2 without initial narrowing restenosis). Seven patients developed recurrent symptoms following their second angioplasty, compatible with restenosis, but did not undergo repeat angiography and were also excluded (4 with initial narrowing restenosis and 3 without initial narrowing restenosis). The remaining 113 patients form the study population, 71 of whom developed restenosis after their initial angioplasty requiring repeat angioplasty at the initial narrowing site (group I), and 42 patients who did not develop restenosis after their initial angioplasty (group II) (Figure 1).

Patients were followed clinically for the recurrence of symptoms for a minimum of 6 months after angioplasty of their new narrowing(s). All patients in the study group who were thought to have developed restenosis on clinical grounds underwent angiography. Follow-up information was obtained by a trained data technician who telephoned each patient 6 and 12 months following angioplasty of the new lesion. No patients were lost to follow-up or died during the follow-up period.

Successful angioplasty was defined as a ≥40% improvement in the luminal diameter of the stenosis with a final stenosis <50%, without myocardial infarction, coronary artery bypass surgery or death. Restenosis was defined by the presence of a ≥50% narrowing based on caliper measurement or visual estimation in orthogonal or near orthogonal views at the site of the previous angioplasty. Because angiography was generally only performed in patients with signs or symptoms suggestive of restenosis, the restenosis rates represent angiographically confirmed clinical restenosis. Multivessel disease was defined as the presence of a ≥70% narrowing in 1 major coronary artery or major branch, and at least 1 additional narrowing ≥50% in another major coronary artery or its major branch. Hypercholesterolemia was defined as a total serum cholesterol ≥250 mg/dl.

Continuous variables are expressed as mean ± 1 standard deviation. Comparisons between groups were performed using chi-square analysis for discrete variables and Student's t *test for continuous variables. Multivariate analysis using a stepwise logistic regression model was performed using clinical and angiographic variables to determine independent predictors of restenosis among the study patients. Statistical significance was assumed using an α of 0.05.*

The baseline clinical characteristics of patients with and without prior restenosis were similar (Table I). Analysis of the angiographic features of the initial angioplasty revealed several important differences between the 2 groups (Table II). Patients in group I who had developed restenosis had narrowings dilated in the left anterior descending artery significantly more frequently than patients in group II. Conversely, the circumflex and right coronary artery were dilated less frequently than in patients without prior restenosis. There was also a trend toward more frequent vein graft dilation in group I with prior restenosis. However, there were no significant differences in the angiographic characteristics of the new narrowing angioplasty sites between the 2 groups (Table III).

The percentage of patients discharged and maintained on β blockers, calcium blockers, nitrates, aspirin,

dipyridamole and anticoagulants following their new narrowing angioplasty was similar between the 2 groups.

Restenosis of the second angioplasty site occurred at 26 of 85 sites dilated (31%) in group I, and at 15 of 57 sites dilated (26%) in group II (p = not significant) (Figure 2), corresponding to 25 of 71 patients (35%) in group I, and 12 of 44 patients (27%) in group II (p = not significant). The number of patients undergoing catheterization in whom restenosis at the new angioplasty site had not occurred was similar in both groups.

Multivariate analysis revealed that the severity of the pre-procedural stenosis was a weak predictor of restenosis (p = 0.07). Other clinical and angiographic variables (Tables I and III) included in the analysis were not found to be independent predictors of restenosis.

Numerous studies have shown that the frequency of restenosis after repeat dilation of a restenotic narrowing is similar to that following dilation of an atherosclerotic narrowing.[5-7] This study examined a different question: Do patients who have a history of restenosis after dilation of an atherosclerotic narrowing have an increased risk for restenosis following the subsequent dilation of a new atherosclerotic narrowing at another site in the coronary circulation? The results of this study reveal that they do not; restenosis occurred in a similar percentage of patients with a history of restenosis following angioplasty at a different site in the coronary circulation as patients in whom restenosis did not occur.

The explanation for why restenosis occurs 1 or more times after angioplasty in some patients while the coronary arteries remain widely patent in others is poorly understood. Among the constitutional features that are believed to influence the restenosis rate, there are several, including male gender, diabetes and cigarette smoking, which presumably might confer an increased risk of restenosis after all angioplasty procedures among such patients.

There are other theoretical reasons why a history of prior restenosis might be predicted to confer an increased risk of restenosis. If, for example, the immune system influences the inflammatory response to injury of the vessel wall from balloon inflation, patients with an exaggerated response to injury might be expected to repeatedly develop restenosis more frequently than patients without an exaggerated response to injury.

Other investigators have recently performed a similar retrospective databank analysis of 90 patients who underwent a second angioplasty of an atherosclerotic narrowing, and reported that restenosis occurred significantly more frequently among patients who had previously developed restenosis: 50% (20 of 40) compared to 22% (11 of 50) among patients without prior restenosis.[8] Our results indicate that patients with 1 or more episodes of restenosis are *not* more likely to develop restenosis after dilation of a new atherosclerotic lesion. The explanation for the disparate findings between the 2 studies is not clear. In the study of Bresee et al,[8] the restenosis rate among patients with prior restenosis was 50%, a higher clinical restenosis rate than has previously been reported. In addition, patients who had prior restenosis had more severe coronary artery disease as evidenced by their greater incidence of multivessel disease, greater number of narrowings dilated, and more rapid progression to symptoms. The possibility that more subclinical episodes of restenosis were detected in the group with prior restenosis as a result of the need for more frequent angiography cannot be excluded; further studies are needed to confirm or refute these findings.

A limitation of this study is that it is a retrospective data bank analysis of a relatively small number of patients. Angiography was performed only in patients in whom it was clinically suspected, and therefore the true percentage of patients with angiographic restenosis is not known for the entire population who underwent coronary angioplasty.

These data are the first to suggest that restenosis following angioplasty at an initial site does not appear to have a major influence on the probability of developing restenosis after a subsequent angioplasty of a new narrowing at a different coronary site. These results support the concept that the most important factors associated with restenosis are related to lesion and procedural characteristics, and that constitutional factors are of less importance. When asked to consider angioplasty in patients who have already had angioplasty followed by 1 or more episodes of restenosis, it appears that such patients may

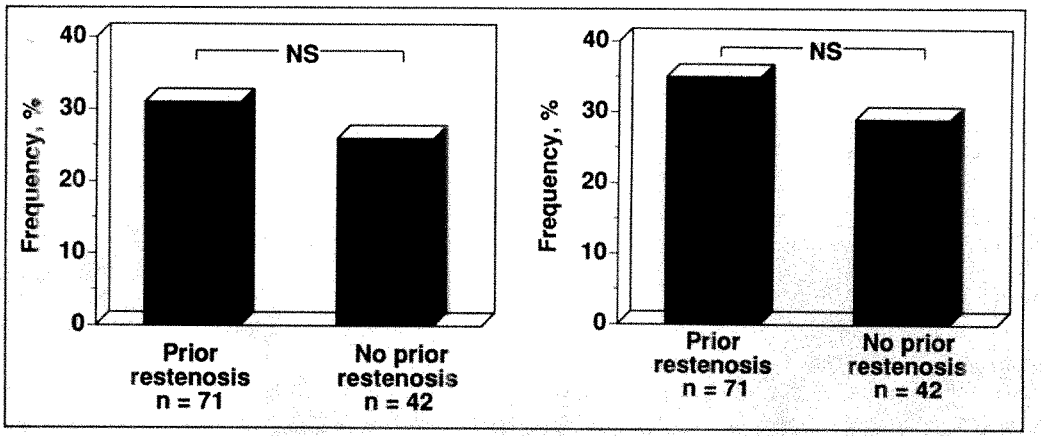


FIGURE 2. The occurrence of restenosis expressed as the percentage of narrowings with restenosis *(left)* and percentage of patients with restenosis *(right)*. NS = not significant.

be reassured that their risk of restenosis does not appear to be significantly higher than the risk among patients who did not develop restenosis after a prior angioplasty.

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Effect of Activity on Circadian Variation in Time of Onset of Acute Myocardial Infarction

John Zornosa, MD, Martha Smith, MD, and William Little, MD

There is a circadian variation in the onset of acute myocardial infarction (AMI) with the peak incidence occurring between 6:00 A.M. and 12:00 A.M. Muller et al[1] proposed that this increased frequency of AMI in the morning is due to the circadian variation of potential triggers of plaque rupture and development of occlusive thrombosis. These potential triggers of AMI include morning surges of cortisol and catecholamines, increases in blood pressure and heart rate, as well as increases in platelet aggregability,[2] blood viscosity,[3] and vasomotor tone in conjunction with diminished fibrinolytic activity.[4] The peak incidence of AMI occurs somewhat later in the morning (10:00 A.M. to 12:00 A.M.) than the peak activity of most of the potential triggers that occur between 6:00 A.M. and 9:00 A.M.[5] Exertion enhances the potential adverse effects of all these potential triggers of AMI. Thus, we hypothesized that baseline resting circadian variation of potential triggers of AMI would have the greatest effect on AMI occurring in the absence of exertion. If this hypothesis is correct, AMI not associated with exertion would have a peak incidence coinciding more closely with the peak adverse effects of the potential triggers in the early morning. Accordingly, this study was undertaken to evaluate prospectively the influence of activity at the onset of AMI to the circadian variation in the time of onset of AMI.

Consecutive patients admitted to North Carolina Baptist Hospital with AMI were interviewed within 48 hours of admission. AMI was defined as significant elevation of creatine kinase-MB (total creatine kinase >250, MB >5%). Twenty-three patients were excluded because their clinical histories were judged to be unreliable. Two hundred ninety-four patients were evaluated (34% anterior, 28% inferioposterior, 38% non-Q-wave AMIs). The time of onset of AMI was quantitated as the time of onset of chest pain. Patients were questioned regarding their activity within 30 minutes before pain onset. Activity was graded as sleep/rest (<3 METs), mild exertion (3 to 5 METs) and moderate to marked exertion (>5 METs) using a previously described format.[6] Patients were then classified into 2 groups: those who were asleep or at rest were classified as "No Exertion" and those participating in mild or greater exertion (>3 METs) as "Exertion." Time of AMI was tabulated by 2-hour intervals, beginning 1 minute after the hour.

The chi-square test was used to compare the distribution of AMI for all patients, and then for the exertion and no exertion groups. All patients were grouped together to analyze the significance of circadian variation, comparing frequency during four 6-hour intervals (12:01 A.M. to 6:00 A.M., 6:01 A.M. to 12:00 A.M., 12:01 P.M. to 6:00 P.M., and 6:01 P.M. to 12:00 P.M.). Each 6-hour interval was further subdivided into 2-hour intervals, beginning 1 minute after the hour. Patients were then separated into exertion and no exertion groups and again analyzed for circadian variation in a similar manner. AMI occurring between 12:00 P.M. and 6:00 A.M. were then excluded and the 2 groups were again compared.

In 232 patients (79%), AMI occurred in the absence of exertion. In the remaining 62 patients, AMI was temporally associated with mild exertion (n = 53), or marked exertion (n = 9). There were no significant differences in age, sex distribution or clinical characteristics between patients with exertionally or nonexertionally related AMI.

Analysis of all 294 patients (Figure 1) showed a peak occurrence of AMI in the morning (6:01 A.M. to 12:00 A.M.) (p <0.005) with the greatest frequency between 10:00 A.M. and 12:00 A.M. The patients with AMI associated with exertion had a peak occurrence during the midday (10:00 A.M. to 12:00 A.M.). Patients with nonexertionally related AMIs had a peak incidence from 6:00 A.M. to 8:00 A.M., earlier in the morning than the entire group. Because of customary sleeping patterns, few patients are active between 12:00 P.M. and 6:00 A.M.; thus, AMIs occurring during this time period were excluded and the groups were compared. There was still a significant difference in the distribution of AMIs between the 2 groups (p = 0.001).

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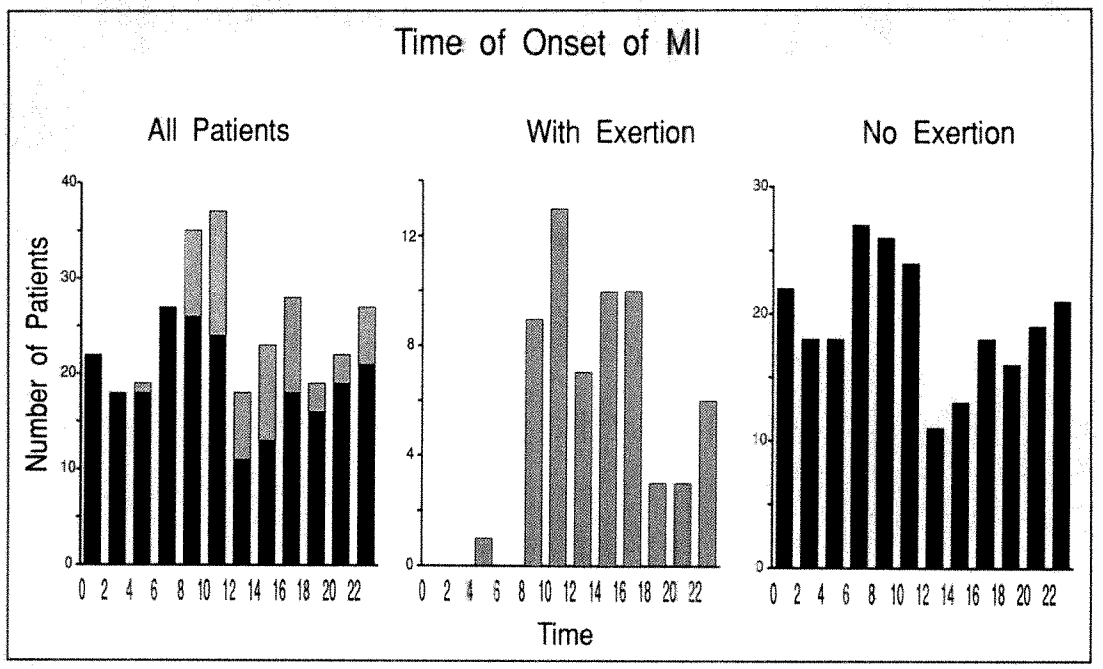


FIGURE 1. Circadian variation in the time of onset of acute myocardial infarction (MI). The peak incidence in all patients was between 10:00 A.M. and 12:00 A.M. The peak incidence of acute myocardial infarction associated with exertion was in the midday. In considering only patients with acute myocardial infarction unassociated with exertion (no exertion), the peak incidence is in the early morning between 6:00 A.M. and 8:00 A.M.

We found that most AMIs occur in the absence of exertion (<3 METs). The peak incidence of these nonexertionally related AMIs is between 6:00 A.M. and 8:00 A.M. This is coincident with the peak activity of many potential triggers of AMI which include surges in heart rate, blood pressure, catecholamines, cortisol, platelet aggregability, coronary vascular tone, plasma viscosity, and fibrinolytic activity associated with awakening and assumption of the upright posture. These factors have been termed triggers because of their potential role as precipitants of coronary artery plaque rupture and subsequent thrombosis.[1] Exercise accentuates all of these potential triggers. Thus, it is not surprising that exertion has been associated with the occurrence of AMI and sudden cardiac death.

AMIs associated with exertion occurred throughout the day with a peak occurrence near midday. It is possible that exercise's profound effect on the potential triggers of AMI may overwhelm the circadian variation of their basal levels. Combining patients with exertionally and nonexertionally related AMI shifted the apparent peak incidence of AMI several hours later in the morning, later than the peak activity of most of the presumed triggers. Thus, inclusion of exertionally precipitated AMI appears to partially obscure the early morning peak in AMI and the potential effect of the circadian variation of the triggers.

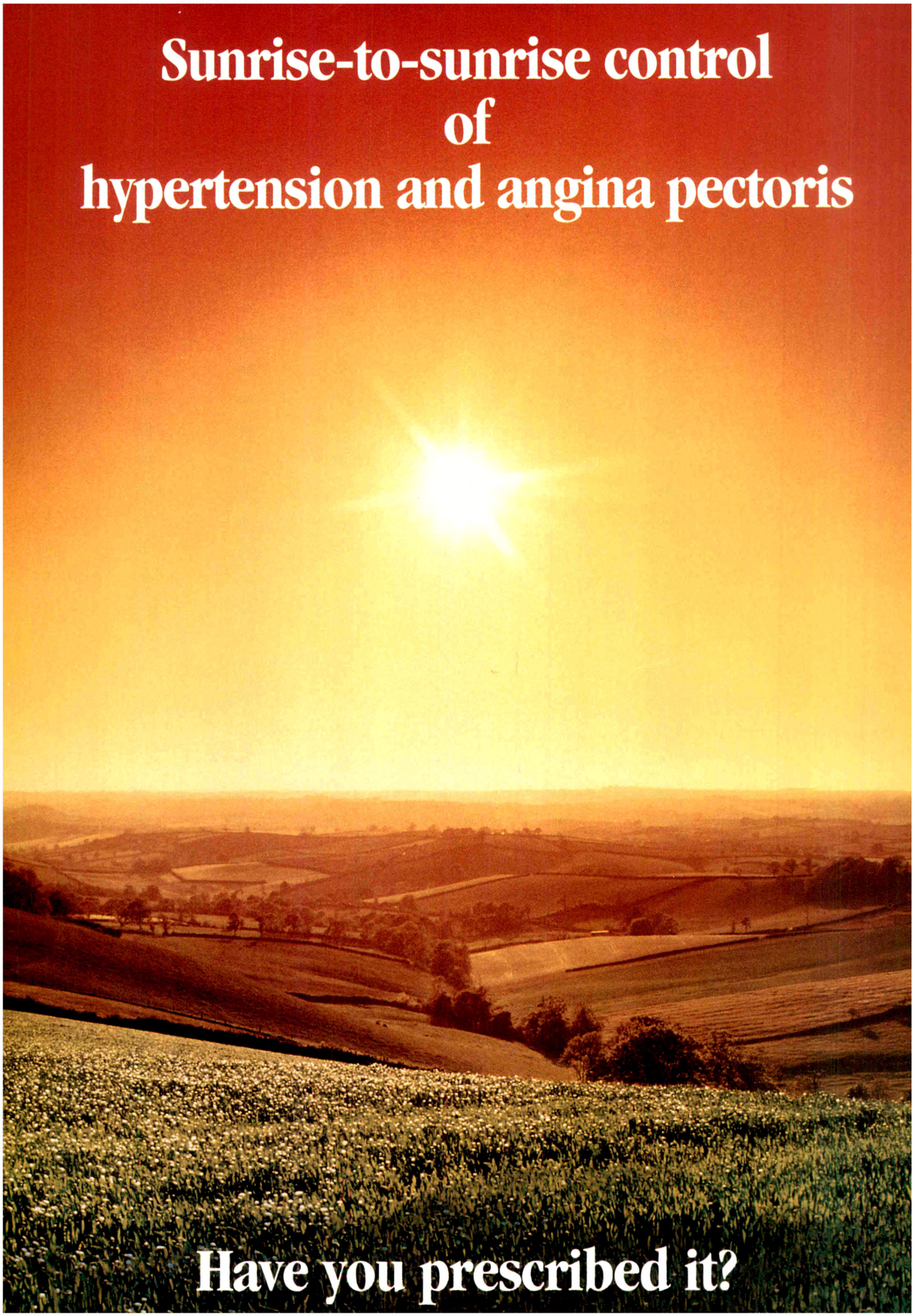
Our study depends on the ability of patients to accurately time the onset of their myocardial infarction. However, this method of timing the onset of AMI correlates well with enzymatic estimation of the time of onset.[5] The early morning surge in the basal activity of most potential triggers of AMI is associated with awakening. Thus, the incidence of AMI may be greater at the time of awakening, which may not always occur early in the morning. However, we did not collect this information, and thus are unable to perform this correction. If we had, we assume that the morning peak incidence of AMI in the absence of exertion would be even more marked.

Since exertion is rare between 12:00 A.M. and 6:00 A.M., this might account for the difference in distribution of the time of onset of AMIs with and without exertion. In contrast, analysis of the data after exclusion of events occurring from 12:00 A.M. to 6:00 A.M. demonstrates that this is not correct.

In conclusion, our study suggests that the circadian variation in the basal level of potential triggers of AMI has its most marked effect on AMI occurring in the absence of exertion. The peak incidence of AMI in the absence of exertion is early in the morning, coincident with the peak level of the potential triggers. Exertionally related AMIs occur throughout the day, with a peak incidence in the midday. It is possible that exertionally related changes in the potential triggers of AMI overcome the basal variation in these triggers, supporting the speculation that exertion may trigger AMI.

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Sunrise-to-sunrise control of hypertension and angina pectoris



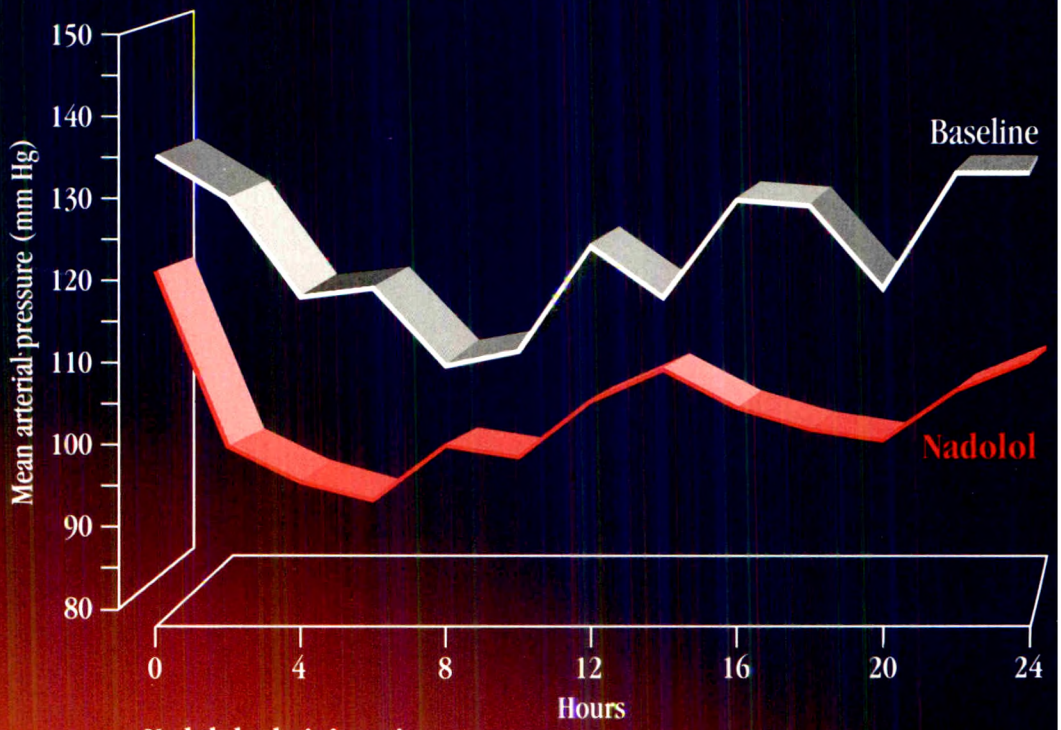
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True Once-daily control

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✓ hypertension[1]



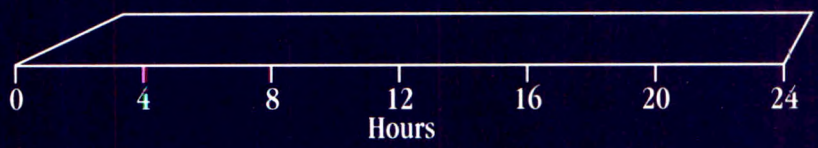
Nadolol administration

24-Hour data from 7 hypertensive patients.
Nadolol doses 80 mg to 320 mg QD.

– Adapted from Mancia G, et al

✓ angina pectoris[2]

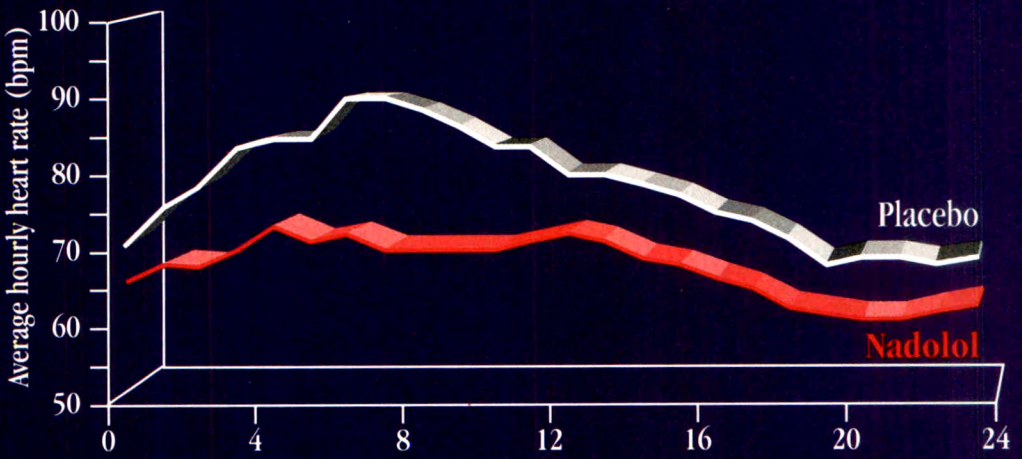
Efficacy established at 3 hours . . . maintained at 24 hours



Eighteen patients were tested on treadmill at 3 and 24 hours after ingestion of nadolol (40-160 mg QD).

– Adapted from Kostis JB, et al.[2]

heart rate[3]



Randomized, double-blind, placebo-controlled, crossover study in 16 patients with effort angina. Mean dosing time nadolol: 9:36 AM.

– Adapted from Kostis JB, et al.[2]

CORGARD® *(nadolol)* *40 mg tablets*

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CORGARD® TABLETS
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DESCRIPTION: CORGARD (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure–Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal–Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)–PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery–Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart-beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia–Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis–Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal Function–Use nadolol with caution (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients–Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign of impending failure. Advise patients in event of missed doses.

Drug Interactions–Concurrent administration may result in interactions with: Anesthetics, general—exaggeration of the hypotension induced by general anesthetics (see WARNINGS, Major Surgery). Antidiabetic drugs (oral agents and insulin)–hypoglycemia or hyperglycemia; adjust antidiabetic drug dosage accordingly (see WARNINGS, Diabetes and Hypoglycemia). Catecholamine-depleting drugs (eg, reserpine)–additive effect; monitor closely for hypotension and/or excessive bradycardia.

Response to Treatment for Anaphylactic Reaction–While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility–In 1- to 2-year oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy Category C–In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogen potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus. Neonates of mothers who received nadolol at parturit have exhibited bradycardia, hypoglycemia, and associated symptoms.

Nursing Mothers–Nadolol is excreted in human milk. Exercise caution when nadol is administered to a nursing woman.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular–Bradycardia with heart rates of less than 60 beats per minute occu commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have bee reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**–Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**–Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**–Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**–Each of the followin reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasa stuffiness; sweating; tinnitus; blurred vision; infrequent reversible alopecia.

The following adverse reactions have been reported in patients taking nadolol and/c other beta-adrenergic blocking agents, but no causal relationship to nadolol has been established. **Central Nervous System**–reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characteriz by disorientation for time and place; short-term memory loss, emotional lability with sligh clouded sensorium; decreased performance onneuropsychometrics.

Gastrointestinal–mesenteric arterial thrombosis; ischemic colitis; elevated liver enzyme

Hematologic– agranulocytosis;thrombocytopenic or nonthrombocytopenic purpura. **Allergic**–fever combine with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**–pemphigoid rash; hypertensiv reaction in patients with pheochromocytoma; sleep disturbances; Peyronie's disease. The oculomucocutaneous syndrome associated with practol has not been reported with nadolol.

OVERDOSAGE: Nadolol can be removed from the gen circulation by hemodialysis. In addition to gastric lavage employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia–Administer atropine (0.25 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure–Administer a digitalis glycoside an diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension–Administer vasopressors, eg, epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm–Administer a $beta_2$-stimulating age and/or a theophylline derivative.

DOSAGE–For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris**, usual initial dose is 40 mg qd; may be gradually increased in 40 to 80 mg increments a to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenanc dose is 40 or 80 mg qd (doses up to 160 or 240 mg daily may be needed). If treatment is to be discontinued, redu dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension**, usual initial dose is 40 mg qd; gradually increase in 40 to 80 mg increments until optim blood pressure reduction is achieved; usual maintenance dose is 40 or 80 mg qd (doses to 240 or 320 mg daily may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert f dosage in these patients.

For full prescribing information consult package insert.

HOW SUPPLIED: In scored tablets containing 20, 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100. The 40 mg, 80 mg, and 120 mg tablets are available in bottles o 1000 tablets. The 20 mg, 40 mg, and 80 mg tablets are also available in Unimatic® unit-dose packs of 100 tablets.

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Bronchocoronary Collateral Circulation in Patients with Three-Vessel Coronary Artery Disease and Normal Left Ventricular Function

Simon Weber, MD, Gérard Pasquier, MD, Yves Martin-Bouyer, MD, Marc Riquet, MD, Philippe D'Athis, MD, Lisa Naditch, MD, and François Guerin, MD

Preservation of left ventricular systolic function in patients with severe proximal 3-vessel coronary artery disease is not uncommon. This discrepancy between a markedly decreased nutritional flow and a preserved contractility raises the question of a possible collateral blood supply to the myocardium through anastomosis between coronary vessels and other intrathoracic circulations. This possibility is substantiated by the observation in some patients during coronary surgery of a back flow of blood in the coronary artery during cardioplegia despite cross clamping of the aorta, indicating the presence of collateral circulation from an extracardiac origin. Anastomosis between the bronchial and the coronary arteries has been found in several anatomic studies[1-4] and have been documented at angiography.[5] Furthermore, disruption of the suture of the bronchial or tracheal anastomosis is less frequent after combined heart lung transplantation than after lung transplantation, probably as a consequence of anastomosis between the coronary and bronchial circulations.[6] These observations led us to investigate the possibility of a bronchocoronary collateral circulation in patients with 3-vessel disease and normal left ventricular function.

We studied 13 patients with a coronary stenosis <90% (assessed by digitalization) proximal to the emergence of any major branch on the 3 coronary vessels and with a normal (>60%) ejection fraction at angiography; 8 subjects with normal coronary arteries served as control subjects. At the end of conventional coronary arteriography, contrast medium (iopamidol, 10 ml) was injected in the ostia of the bronchial arteries after selective catheterization; optical density was then monitored at the apex of the left ventricle by digitalized angiography. We hypothesized that if functionally significant bronchocoronary anastomoses did exist, a rapid increase in optical density at the level of the ventricular walls should result from injection of contrast medium in the bronchial arteries (Figure 1). Acquisition was performed with an 8 bit 512 × 512 matrix ADAC DPC system at 25 frames per second. Optical density was assessed on a 256 level scale (0 to 255 arbitrary units). Two areas of interest were studied: a rectangular surface involving 311 pixels positioned at the apex of the left ventricle whose blood

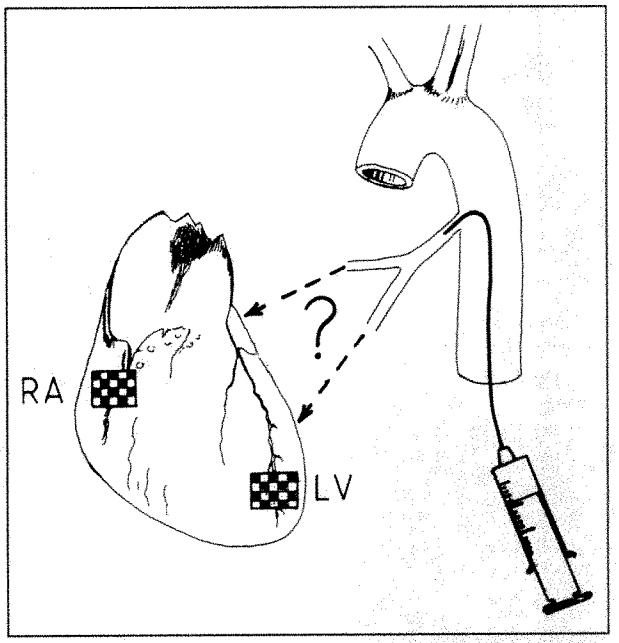


FIGURE 1. Contrast medium injection in the bronchial arteries should result in increased optical density of the apex of the left ventricle (LV) if bronchocoronary anastomoses are present. RA = right atrium.

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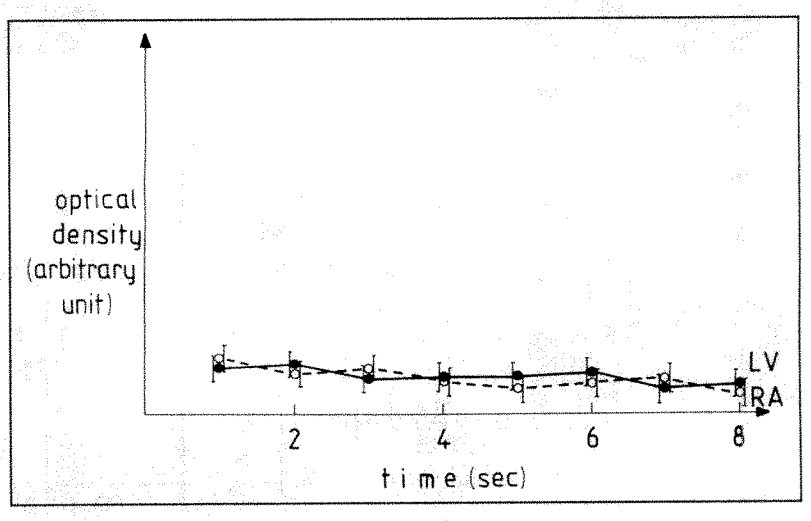


FIGURE 2. Time course of optical density in 8 normal subjects. LV = left ventricle; RA = right atrium.

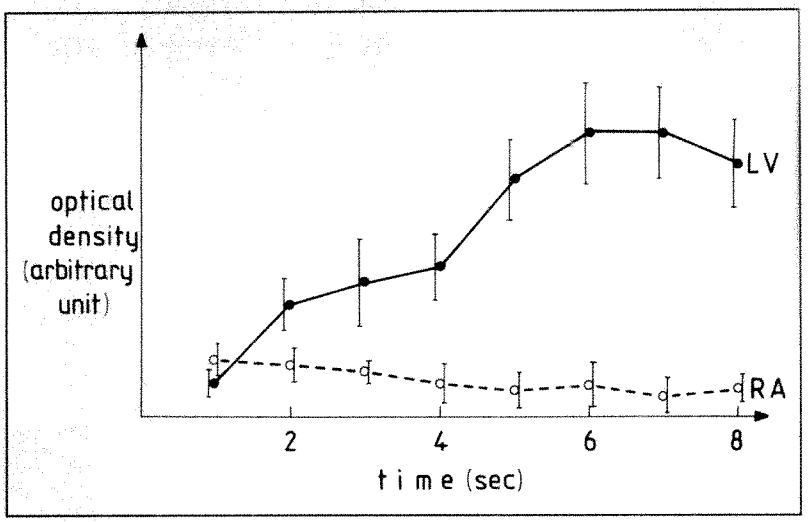


FIGURE 3. Time course of optical density in 13 subjects with 3-vessel disease. LV = left ventricle; RA = right atrium.

supply usually originates from branches of 3 major coronary arteries, and at the right atrial level as a reference. Optical density was monitored in these 2 zones during 8 seconds after contrast medium injection; 200 measurements were thus available to plot an optical density versus time curve. The time course of optical density at the right atrial level and at the apex of the left ventricle were then compared by analysis of variance for repeated measurements. In the 8 control subjects (Figure 2), optical density curves were not different in the right atria and in the left ventricle. Conversely, in the 13 patients, the mean optical density progressively increased in the apex of the left ventricle throughout the 8-second acquisition period, whereas it remained unchanged at the right atrial level (Figure 3); the increase in left ventricular optical density was signifiant ($p < 0.005$) and indicates the presence of myocardial perfusion by a bronchocoronary collateral circulation. Furthermore, 2 patients had direct visualization of epicardial coronary arteries through this bronchocoronary collateral circulation.

Anastomoses between the bronchial and coronary circulation are common occurrences and precede the development of obstructive coronary stenosis since they can be found in subjects without coronary atheroma and even in infants.[1-4] Because of the lack of increase in optical density at the left ventricular level in the 8 control subjects, their contribution to myocardial perfusion is nonexistent or minimal as long as the coronary arteries remain normal. Severe proximal stenoses cause a pressure gradient between the bronchial circulation and the distal coronary vascular bed, which in turn provides the driving force for an increased collateral flow that may become a significant source of blood supply to the ischemic myocardium.

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Persistent Inappropriate Sinus Tachycardia After Radiofrequency Current Catheter Modification of the Atrioventricular Node

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Atrioventricular (AV) junctional reentrant tachycardia (JRT) is the most frequent cause of paroxysmal supraventricular tachycardia.[1] Recently, radiofrequency current delivered through a transvenous catheter was used to modify AV nodal properties so that AVJRT is no longer inducible while preserving normal AV nodal conduction.[2-4] This technique has produced high success rates with relatively few complications. In this report, we present a previously unreported complication observed in 3 patients undergoing AV node modification using radiofrequency current: persistent, inappropriate and symptomatic sinus tachycardia.

Eight consecutive patients with long-standing, symptomatic AVJRT were referred to our institution for radiofrequency current catheter modification of the AV node between July 1, 1990, and December 31, 1990, and were included in this analysis. Clinical data were obtained retrospectively from office and hospital records.

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Heart rate data before hospitalization were obtained from ≥5 entries in office or hospital records; heart rate data for the 48- to 72-hour period immediately after the procedure were obtained from intensive care records recorded hourly (mean number of recordings/patient 43 ± 12). Furthermore, 24-hour Holter monitor recordings during normal activity were obtained 4 to 6 weeks after the modification procedure in all 3 patients with inappropriate sinus tachycardia.

All patients underwent standard electrophysiologic studies (without cardiac medications) before, 48 to 72 hours after (further AV node modification was performed if AVJRT remained inducible), and 2 to 4 months after the modification procedure. Standard techniques for the induction of supraventricular tachycardia were used.[5] Isoproterenol was administered to all patients during these studies. In 1 patient with inappropriate sinus tachycardia, the intrinsic heart rate was determined by administering intravenous propranolol (0.2 mg/kg) and atropine (0.4 mg/kg)[6] during the 4-month follow-up electrophysiologic study.

Radiofrequency energy was delivered by a large-tip (4 mm), steerable, 7Fr quadripolar catheter as a continuous unmodulated sine-wave output at 350 kHz from an electrosurgical unit (model RFG-3B, Radionics, Burlington, Massachusetts). The anterior approach, as described by Lee et al,[3] was used in all patients. The end point of radiofrequency ablation was to prevent the induction of sustained supraventricular tachycardia.

Inappropriate sinus tachycardia was defined as sinus rhythm at rates >100 beats/min occurring at rest without typical physiologic or hemodynamic precipitants such as pain, fever, hypovolemia, hypotension, hypoxemia or hyperthyroidism. P-wave morphology was identical to that in normal sinus rhythm, and heart rates demonstrated a normal diurnal variation as would be expected for sinus rhythm (Figure 1). Three of 8 patients who underwent radiofrequency current catheter modification of the AV node developed persistent palpitations associated with inappropriate sinus tachycardia after the radiofrequency modification procedure and constitute group I. The 5 patients who did not develop inappropriate sinus tachycardia constitute group II.

Data are expressed as mean and range. Comparisons of continuous variables between the 2 groups were performed using unpaired t *tests; comparisons within each group were performed using paired* t *tests. Comparisons of discrete variables were performed using Fisher's exact test. Significance was defined as $p < 0.05$.*

The mean age for patients in group I was 48 years (range 26 to 64). The mean age for patients in group II was 44 years (range 33 to 79). Clinical characteristics did not differ significantly between the 2 groups (Table I). The mean baseline heart rates were 85 beats/min (range 74 to 92) for group I, and 79 beats/min (range 66 to 93) for group II. At baseline electrophysiologic testing, sinus cycle length, PR interval, AH interval, AV node Wenckebach cycle length and effective refractory period, and

TABLE I Clinical Characteristics and Electrophysiologic Variables for Patients Undergoing Atrioventricular Node Modification

Patient	ST	Age (yr) & Sex	Medical History	Pre-Procedure Medications	Baseline HR, Mean (range)	Post-Procedure HR, Mean (range)	Number of RF Applications	Pre-Procedure PR (ms)	Post-Procedure PR (ms)
1	+	64F	MVP, MR	VER, QUIN	88 (84–90)	101 (94–144)	37	180	235
2	+	55F	DM, HTN, CAD	VER, DISO	92 (79–108)	110 (100–150)	28	150	200
3	+	26F	MVP	DIG, BB	75 (65–88)	95 (78–116)	41	120	185
4	–	39M	—	VER	70 (60–78)	85 (62–100)	21	155	190
5	–	33M	—	VER	79 (64–96)	91 (81–104)	20	170	205
6	–	35M	—	VER	77 (67–91)	78 (64–96)	30	270	440
7	–	79M	HTN	DIG, VER	73 (55–90)	54 (44–83)	24	200	230
8	–	36F	MVP	VER	93 (75–101)	86 (69–97)	21	120	230

BB = β blocker; CAD = coronary artery disease; DIG = digoxin; DISO = disopyramide; DM = diabetes mellitus; HR = heart rate; HTN = hypertension; MR = mitral regurgitation; MVP = mitral valve prolapse; PR = PR interval; QUIN = quinidine; RF = radiofrequency; ST = sinus tachycardia; VER = verapamil.

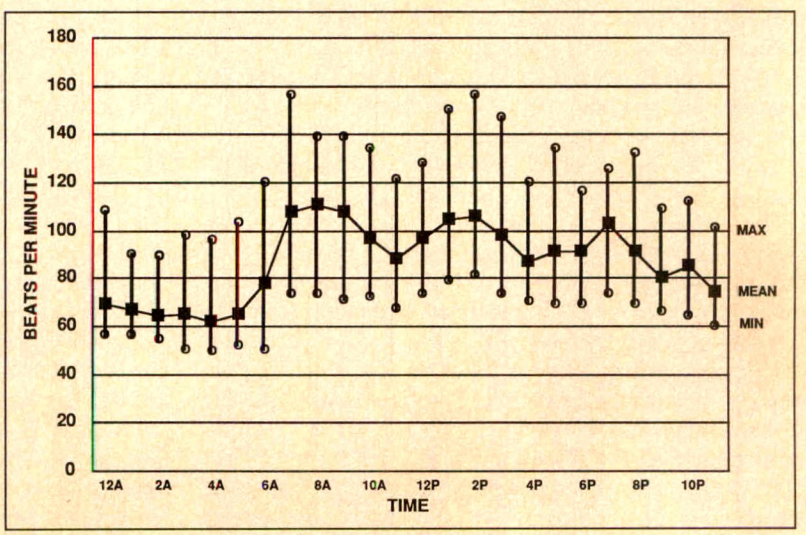


FIGURE 1. Hourly heart rate data of 26-year-old woman (patient 3) with inappropriate sinus tachycardia from Holter monitoring during routine daily activities 6 weeks after radiofrequency current modification of atrioventricular node. MAX = maximum heart rate; MEAN = mean heart rate; MIN = minimum heart rate.

ventriculoatrial block cycle length did not differ significantly between the 2 groups.

One patient in group I, and 2 in group II underwent 2 modification procedures for successful treatment of AVJRT; however, total procedural time did not differ between the 2 groups. Mean voltage and current, as well as mean duration of radiofrequency energy application did not differ significantly between the 2 groups. The only procedural difference between the 2 groups was mean number of radiofrequency applications (35 [28 to 41] for group I vs 23 [20 to 30] for group II; $p = 0.02$).

Immediately after the modification procedure, 3 patients developed palpitations at rest associated with sinus tachycardia on cardiac monitoring. Patient 1 had heart rates at rest ranging from 103 to 144 beats/min, patient 2 had them at 110 to 146 beats/min, and patient 3 had them at 88 to 116 beats/min. Mean heart rate for group I during this period was 103 beats/min. Mean heart rate for group II during the same period was significantly lower (78 beats/min, range 46 to 114; $p < 0.01$). In both groups, all patients were afebrile and normotensive without evidence of orthostatic hypotension, and no patient had a change in hematocrit >2% from baseline values. In group I, all patients had normal arterial blood gas measurements and normal thyroid function tests. Two of the 3 patients in group I underwent 24-hour urinary collections for metanephrines (which were normal).

Treatment with intravenous β-blocker therapy was initiated 48 to 56 hours after the onset of palpitations in 2 of the 3 patients who developed inappropriate sinus tachycardia. In both cases, this treatment resulted in slowing of heart rates and in at least partial resolution of symptoms. Both patients were discharged on daily atenolol, but continued to have infrequent palpitations with minimal exertion. Holter monitoring obtained 4 to 6 weeks after the procedure revealed episodes of sinus tachycardia that corresponded to palpitations in all 3 patients. Patient 1 had heart rates up to 114 beats/min (mean 88) with minimal physical exertion, patient 2 up to 108 beats/min (mean 92), and patient 3 up to 156 beats/min (mean 86) (Figure 1). No evidence of supraventricular tachycardia was noted in these studies. In clinical follow-up since that time (mean 9 months), episodic palpitations decreased in frequency and duration in all 3 patients. However, attempts to wean β-blockers were unsuccessful, because of recurrence of palpitations.

At electrophysiologic testing 2 to 4 months after the modification procedure, sinus cycle length, PR interval, AH interval, AV node Wenckebach cycle length and effective refractory period, and ventriculoatrial block cycle length did not differ significantly between the 2 groups. There was significant PR interval prolongation compared with at baseline in group I (Table I). In 1 patient in group I (patient 2), AVJRT was induced at the follow-up study with double-atrial extrastimuli during isoproterenol infusion.

Sinus cycle length, corrected sinus node recovery time and chronotropic response to isoproterenol were similar in both groups at follow-up testing. For group I, mean sinus cycle length at baseline was 702 ms (range 585 to 800) and decreased to 465 ms with isoproterenol; mean corrected sinus node recovery time was 165 ms (range 150 to 195). For group II, mean sinus cycle length at baseline was 824 ms (range 715 to 1,030) and decreased to 528 ms with isoproterenol; mean corrected sinus node recovery time was 123 ms (range 95 to 210). The intrinsic heart rate was determined in 1 patient from group I (patient 2). Intravenous propranolol administered alone increased the sinus cycle length to 640 ms from a baseline of 585. After the administration of intravenous propranolol and atropine, sinus cycle length decreased to 610 ms. Thus, the intrinsic heart rate was 98 beats/min. The predicted intrinsic heart rate for this patient (aged 55 years), determined using the method of Jose and Taylor,[6] was 86 ± 16 beats/min.

Inappropriate sinus tachycardia after radiofrequency modification of the AV node has not been previously reported as a complication of this procedure. However, in a series of patients undergoing radiofrequency modification of the AV node reported by Lee et al,[3] one patient who had a successful AV nodal modification underwent complete His bundle ablation for what was thought to be preexisting inappropriate sinus tachycardia. Although sinus tachycardia may have been a preexisting condition in this patient, the differentiation of symptoms due to inappropriate sinus tachycardia from those due to AVJRT may be extremely difficult. Thus, it is possible that sinus tachycardia developed only after the AV nodal modification procedure.

In our study, there appears to be an association between inappropriate sinus tachycardia and increased number of applications of radiofrequency energy in the region of the AV node. The relatively large number of applications of energy present in both groups is a manifestation of the energy titration technique that we used. For example, successive applications of 30, 40 and 50 V at the same catheter position were counted separately. This technique was used to minimize the risk of complete AV block resulting from radiofrequency energy application. Despite the relatively large number of energy applications in both groups, patients who developed sinus tachycardia received significantly more applications of radiofrequency energy during the modification procedure. Because of the small number of patients we cannot exclude a gender difference in the susceptibility to inappropriate sinus tachycardia.

The mechanism of inappropriate sinus tachycardia after radiofrequency modification of the AV node is unknown. It is unlikely that the radiofrequency modification procedure induced direct damage to the sinus node, because this structure is remote from the site of ablation. This is confirmed by the normal sinus node recovery times in both groups. Therefore, it is likely that the sinus tachycardia is secondary to autonomic influences on the sinus node. Although the precise anatomy of the parasympathetic nerve supply to the human heart remains to be defined, extensive work has been performed in canine[7] and bovine[8] hearts. From this and other studies,[9,10] it is known that postganglionic parasympathetic fibers course through the region of the AV node to innervate the sinoatrial node. It is possible that radiofrequency lesions in the region of the AV node may result in damage to these fibers and decrease parasympathetic control of sinus activity. In the patient in whom the intrinsic heart rate was

determined, the addition of atropine to the propranolol-treated heart only minimally changed the sinus cycle length (640 to 610 ms). This is consistent with some decrease in vagal effect on the sinus node.

An alternative hypothesis is that effective sympathetic tone at the sinoatrial node is increased. It is possible that the atrial injury produced by radiofrequency energy can cause the same increase in β-adrenergic receptor density that is seen in myocardial ischemia.[11] Furthermore, it is possible that the atrial injury produced by the radiofrequency modification procedure induces the local release of adrenergic neurotransmitters without producing systemically detectable levels. However, it seems unlikely that limited atrial injury would produce a sustained increase in β-adrenergic receptor density or sustained local release of neurotransmitters.

Another potential explanation for inappropriate sinus tachycardia in these patients is that they had preexisting paroxysmal sinus tachycardia unrelated to radiofrequency ablation, which was revealed by discontinuation of antiarrhythmic medications. However, this seems unlikely because: (1) no history of paroxysmal sinus tachycardia was noted before the initiation of drug therapy, and (2) paroxysmal sinus tachycardia is a rare disease and its coexistence with AVJRT seems even more improbable.

In this report, the only technique used for AV junctional modification was the anterior or fast pathway approach. It is not known if inappropriate sinus tachycardia may also develop when the posterior or slow pathway approach is used, nor is it known if improvements to the procedure will affect the development of this potential complication.

Thus, 3 of 8 patients who developed symptomatic, inappropriate sinus tachycardia after radiofrequency current catheter modification of the AV node were presented. This is the first report of this complication. The symptoms ranged from mild to debilitating palpitations and often needed treatment with β blockers that are effective in controlling symptoms. It appears that in most patients the inappropriate sinus tachycardia may resolve over a prolonged time period, but may remain as a significant long-term problem needing treatment. It appears as if autonomic dysfunction may have an important role in the etiology of this complication; however, the role of other, unexplained factors cannot be excluded. Continued follow-up will be needed to establish the natural history of this complication, and further work is needed to elucidate its cause.

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Determinants of Impedance During Radiofrequency Catheter Ablation in Humans

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Radiofrequency catheter ablation has become the treatment of choice for selected patients with paroxysmal supraventricular tachycardia due to atrioventricular node reentry or the Wolff-Parkinson-White syndrome.[1–3] Despite encouraging results described in several series, the optimal energy delivery strategy has not been defined. Lesion formation occurs during radiofrequency ablation as the result of resistive heating at the electrode-tissue interface.[4] The magnitude of heat generation is proportional to power density at the point of contact.[5] Electrosurgical units currently being used for radiofrequency ablation have a low source impedance and therefore approximate constant voltage sources. With such a device, one preselects a given output voltage. Applied power is proportional to the square of this output voltage and is inversely proportional to the load impedance imposed by the ablation catheter, patient and indifferent electrode. Thus, the effectiveness of any given energy application may be influenced by the impedance of the system. This study characterizes impedance during radiofrequency catheter ablation in humans, and defines the relation between clinical and ablation parameters, and measured impedance.

Twenty-seven patients (15 men [55%], mean age 42 ± 19 years) undergoing radiofrequency catheter ablation in July and August 1991 were included in this study. The procedure was performed using a protocol approved

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TABLE I Characteristics of Patients Undergoing Radiofrequency Catheter Ablation

Patient	Age (yr) & Sex	Heart Disease	Diagnosis	Ablation Site
1	15F	0	WPW	Right posteroseptal
2	17F	0	WPW	Right anteroseptal
3	17M	0	WPW	Left posterolateral
4	18M	0	WPW	Right posteroseptal
5	19M	0	WPW	Left lateral
6	19F	0	WPW	Mid-septal
7	26F	0	WPW	Right posteroseptal
8	30F	0	WPW	Right posteroseptal
9	32M	0	WPW	Right anteroseptal
10	33F	0	WPW	Left lateral
11	38M	0	WPW	Left posterolateral
12	38M	0	WPW	Left lateral
13	41M	0	WPW	Right anterolateral
14	41F	0	WPW	Right anteroseptal
15	46M	0	AVNRT	Fast pathway
16	47F	0	AVNRT	Slow pathway
17	48M	0	AVNRT	Slow pathway
18	49M	0	WPW	Left anterior
19	55M	0	WPW	Left posteroseptal
20	56F	0	WPW	Right anteroseptal
21	65F	0	WPW	Right anteroseptal
22	66F	0	AVN ablation	His bundle
23	70M	0	WPW	Left lateral
24	52M	CAD	AVN ablation	His bundle
25	59M	CAD:CABG	AVN ablation	His bundle
26	67F	CAD	AVNRT	Fast pathway
27	72M	CAD:CABG	VT	Left ventricle

AVN = atrioventricular node; AVNRT = atrioventricular nodal reentrant tachycardia; CABG = coronary artery bypass graft; CAD = coronary artery disease; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

by the human research committee of the University of Michigan Medical Center, and all patients gave informed written consent. Clinical characteristics of this cohort are listed in Table I. Structural heart disease was present in 4 patients. Catheter ablation of an accessory atrioventricular connection was performed in 19 patients, ablation of the atrioventricular junction in 3, and atrioventricular nodal modification for treatment of typical atrioventricular node reentry tachycardia in 4. Patient 21 had an attempt at ablation of microreentrant ventricular tachycardia in the inferobasilar aspect of the left ventricle.

The power source used in this study supplied a continuous, unmodulated output at 500 KHz (EP Technologies, Inc., Mountain View, California). This device, through an interface with a microcomputer (T-1600, Toshiba Electronics, Japan), measures, displays and stores root-mean-square voltage, current, power and impedance during each energy application. To prevent continued current flow after coagulum formation, the device automatically discontinues power delivery if impedance is >300 ohms.

Electrode catheters from 2 manufacturers (Mansfield Scientific, Watertown, Massachusetts, and EP Technologies) were used for ablation. Both catheters had deflectable shafts that were 7Fr in diameter, as well as large (4 mm in length) distal electrodes. Radiofrequency energy was applied between the distal electrode of the ablation catheter and a large surface area adhesive skin electrode (Valleylab, Boulder, Colorado) placed over the left scapula. Techniques for positioning the ablation catheter were described previously.[1,3,6] For interruption of atrioventricular conduction, the catheter was advanced across the tricuspid annulus and manipulated to record the largest His electrogram. Ablation of right free wall and septal accessory pathways was performed by introducing the catheter in the femoral vein and positioning it at a site on the tricuspid annulus with a short local atrioventricular or ventriculoatrial activation time, or both. A retrograde aortic approach was used for left free wall accessory pathways. The catheter was positioned on the ventricular side of the mitral annulus at the site of earliest activation.

The location of the ablation catheter, energy delivery parameters (including voltage, current, power, duration and impedance) and electrophysiologic effects of every radiofrequency application were recorded in all 27 subjects. To determine if impedance was influenced by the size of the patient, body surface area was calculated for each patient using the formula of Dubois.[7] To define the relation between lung volumes and impedance, forced vital capacity was measured within 24 hours of catheter ablation in 18 subjects using a precision handheld spirometer (Boehringer Laboratories, Germany).

The relation between clinical and ablation parameters, and impedance was analyzed using multivariate regression. A value <0.05 was considered statistically significant.

In all, 257 applications of radiofrequency energy were delivered during the course of catheter ablation in the 27 patients. Mean impedance was 100 ± 10 ohms (range 77 to 132). There was a significant, direct correlation between body surface area and impedance (r^2 = 0.44, p = 0.0001; Figure 1). Forced vital capacity was also independently predictive of impedance (r^2 = 0.39, p = 0.03).

Neither age nor gender correlated with impedance. Impedance during applications that produced conduction block was slightly but significantly less than during ineffective applications (98 ± 9 vs 101 ± 10 ohms; p = 0.01). Applied power did not appear to affect im-

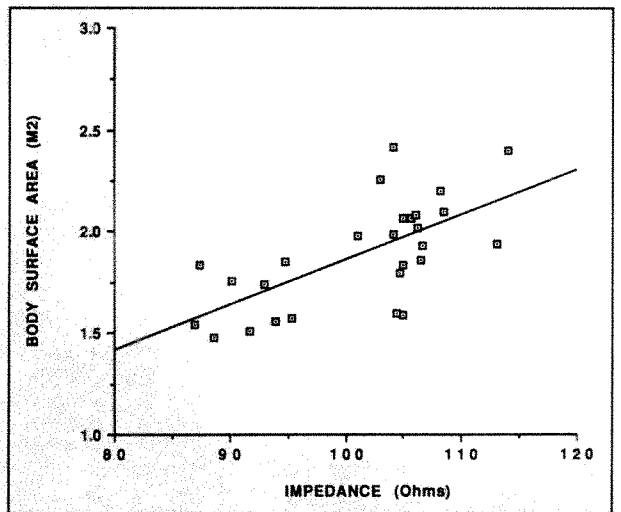


FIGURE 1. Relation between body surface area and impedance in 27 patients undergoing radiofrequency catheter ablation.

pedance, nor was there a difference in impedance between applications in the right heart and those in the left, nor between the 2 types of ablation catheter used.

Impedance during radiofrequency catheter ablation in humans is variable, with a range of 55 ohms noted in this study. Impedance was directly proportional to body surface area and forced vital capacity. Impedance was significantly less during radiofrequency applications that were successful compared with during ineffective applications. No other clinical or energy delivery parameters appeared to affect impedance, nor did the 2 types of ablation catheters used in this study differ significantly.

The volume of a resistive medium interposed between 2 electrodes is proportional to the impedance to alternating current flow. The larger the body surface area, the greater the amount of tissue between the ablating and indifferent skin electrodes. The relation between body size and transthoracic impedance during defibrillation[8] is consistent with this hypothesis.

A study of radiofrequency ablation in the left ventricle in experimental animals showed significantly higher impedances when a conventional distal electrode (2 mm in length, 12.6 mm^2 in surface area) was used compared with a large distal one (3 mm in length, 18.9 mm^2 in surface area).[9] The similar mean impedance values seen with the 2 different types of ablation catheter in the current study probably reflect the fact that distal electrode surface areas were the same.

Impedance during successful radiofrequency energy applications was slightly but significantly lower than during unsuccessful applications. Studies in animals, and a recent clinical report from our laboratory show that tissue heating causes impedance to decrease.[10] This temperature dependence may also explain why effective applications were associated with a lower mean impedance, because some ineffective applications may have been the result of inadequate heating.

It is well known that phasic changes in lung volume with respiration produce corresponding fluctuations in transthoracic impedance. This phenomenon has been used to estimate minute ventilation in activity pacemakers, and for apnea monitoring with cutaneous electrodes.[11-13] The influence of vital capacity seen in this study suggests that the volume of lung parenchyma between the endocardial and indifferent electrodes also significantly affects impedance to current flow during radiofrequency catheter ablation.

The results of this study suggest that the size of the patient can significantly affect impedance during radiofrequency ablation, which may in turn impact on the adequacy of lesion formation. For example, 60 V applied to a small patient in whom the impedance is 90 ohms would result in delivery of 40 W. In contrast, 60 V applied in a larger patient in whom the impedance is 120 ohms would result in delivery of only 30 W. Therefore, if a constant voltage radiofrequency generator is used for catheter ablation, the output voltage may need adjustment commensurate with the impedance of the patient.

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Detection of Atrial Tachyarrhythmias by Transesophageal Pacing and Recording at Rest and During Exercise in Children with Ventricular Preexcitation

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Ventricular preexcitation can be associated with symptomatic supraventricular tachyarrhythmias that can appear at rest and during exercise. In adults, transesophageal atrial pacing has been shown to be an effective method to induce supraventricular tachyarrhythmias and to evaluate the degree of risk in this syndrome.[1,2] In Italy, this procedure (mandatory by law) is used at rest and during exercise in competitive athletes to induce atrial fibrillation and to predict its degeneration into ventricular fibrillation by the shortest RR interval between preexcited beats.[3] In the pediatric field, children have undergone transesophageal atrial pacing at rest. In this study, we assessed the efficacy of transesophageal atrial pacing in the detection of atrial tachyarrhythmias, and for the effectiveness of therapy at rest and during exercise in children with and without evidence of arrhythmias on routine tests as a possible alternative to invasive electrophysiologic studies.

Between November 1989 and November 1991, we performed transesophageal atrial pacing at rest and during exercise in 21 consecutive children aged >6 years with ventricular preexcitation. The study was not completed in 3 patients, because of a lack of cooperation. Eighteen children (mean age 11 ± 2.6 years, range 7 to 15) with surface electrocardiographic features of ventricular preexcitation were studied. One patient with mild Ebstein's anomaly, palpitations at rest and dizziness during effort was admitted to the hospital with supraventricular tachycardia. All other patients had no evidence of arrhythmias on resting electrocardiography, Holter monitoring, maximal exercise testing, chest x-ray or echocardiography. Five patients had sustained (>30) palpitations at rest, 2 had sustained palpitations at rest plus infrequent episodes of dizziness during effort, 1 had an episode of syncope during physical activity, and 10 were asymptomatic. All patients underwent transesophageal atrial pacing at rest and during exercise after written informed consent was obtained from parents.

All patients were studied using the following protocol: (1) introduction of the catheter from the nose into the esophagus during bipolar recording to the position where the maximum amplitude of the atrial potential was recorded; (2) determination of atrial pacing threshold using a stimulus duration of 10 to 13 ms (to ensure consistent atrial capture, stimulation was performed with an amplitude 20 to 30% higher than at threshold); (3) stimulation at rest with 1, 2 or 3 premature stimuli after 8 stimuli at cycle lengths of 600, 450 and 350 ms, respectively; (4) stimulation at rest with bursts of stimuli at decreasing cycle lengths (decreasing 50 ms every 5 seconds, from 600 to 150 ms); (5) maximal upright bicycle exercise stress testing (James protocol)[4]; and (6) stimulation with decreasing cycle length pacing (decreasing 50 ms every 5 seconds, from 300 to 150 ms) at the maximum heart rate previously reached during normal exercise testing.

After 5 half-lives of propafenone (15 mg/kg/day) was initiated, the protocol was repeated in a patient with severely symptomatic tachyarrhythmia induced by the initial transesophageal atrial pacing. Stimulation and recording were performed with a 10Fr quadripolar catheter with interelectrode distances of 20 mm between the 2 proximal electrodes, and 25 mm between the 2 distal ones (Medtronic SP.7505). Only the distal electrodes were used for pacing. A transesophageal stimulator (SEP 3 Bioelectronica) that can deliver pulses of 20 ms duration and 50 mV amplitude, with a maximum rate of 400/min was used for stimulation. A Siemens Cardiostat 3 was used for recording. All exercise testing was performed on a bicycle ergometer (Mijnhardt KEM2). Complete cardiorespiratory resuscitation equipment was available. All patients were fasting for ≥3 hours and had a peripheral intravenous line in place during the study.

Five control subjects (mean age 9.3 years, range 7 to 15) were also tested by transesophageal atrial pacing using the same protocol. These patients had palpitations of <5 seconds, which justified transesophageal atrial pacing, but no other abnormality on the same routine tests as the study group.

The procedure was well-tolerated by each patient. Atrial capture was achieved at rest by an average impulse voltage of 20 mV (range 14 to 25) and by an average impulse duration of 11.6 ms (range 10 to 16), and similar stimuli were always effective during exercise. Transesophageal atrial pacing at rest produced sustained episodes of supraventricular tachycardia in 6 patients (5 with palpitations, and 1 with no symptoms), and an asymptomatic, nonsustained episode of atrial flutter (2:1 and 3:1 conduction through the atrioventricular node) in 1. In 1 patient we induced an asymptomatic, sustained atrial flutter (2:1 conduction through the atrioventricular node and after 2 minutes through the anomalous pathway) after a short episode of atrial fibrillation. Asymptomatic atrial fibrillation was induced in 6 patients (sustained in 3, and very short in 3). Cardioversion was not necessary in any patient, with each episode stopping spontaneously. During exercise, 2 patients with inducible supraventricular tachycardia and palpitations at rest developed supraventricular tachycardia with higher heart rates, shorter ventriculoatrial intervals, and dizziness. One patient had presyncope with the induction of sustained atrial flutter,

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with 1:1 conduction through the atrioventricular node, but had a spontaneous resolution. In this patient, transesophageal atrial pacing after initiation of propafenone therapy induced the same atrial flutter, but the patient was asymptomatic because of 2:1 conduction. Four patients had asymptomatic atrial fibrillation (sustained in 2, and not sustained in 2). No atrial tachyarrhythmia was inducible in the control group either at rest or during exercise.

In the past ten years, various reports describing the correct use and efficacy of transesophageal atrial recording and pacing in the diagnosis and management of reciprocating atrioventricular tachycardia,[5–8] as well as 1 study evaluating the degree of risk for adults with ventricular palpitations were published.[3] In children, transesophageal atrial pacing has been used for acute termination of recurrent atrial tachycardia,[9,10] for diagnosis of tachyarrhythmias,[11,12] for treatment of supraventricular tachycardia[13] and for a study of the development of supraventricular tachycardia in the first year of life.[14]

Other studies found that supraventricular tachycardia or other atrial tachyarrhythmias are inducible only in a low percentage of children with ventricular palpitations during maximal exercise testing.[15] Furthermore, the spontaneous induction of atrial tachyarrhythmias in children with ventricular palpitations occurs infrequently, and sudden death has occurred only in patients with associated congenital heart disease or during digoxin treatment.[16,17] However, atrial flutter or fibrillation seem to be inducible during electrophysiologic studies in about 20% of these patients.[16]

In our study, transesophageal atrial pacing at rest and during exercise was safe and tolerated by 86% of patients. No patient had any damage of the esophagus. Cardiorespiratory resuscitation equipment was not necessary. Transesophageal atrial pacing was effective in revealing the cause of symptoms in most patients, reproducing in the laboratory the same conditions that caused spontaneous induction of supraventricular tachycardia during normal activities. In the 2 patients with palpitations at rest, and dizziness during effort, transesophageal atrial pacing was effective in revealing that the same supraventricular tachycardia was responsible for the 2 different symptomatologies. We believe that this is owing to the influence of adrenergic tone on the conduction and refractoriness of the reentrant circuit, and to the rate-dependent conduction of the accessory pathway.[11] The patient who had syncope during play, and presyncope during testing had the etiology of his symptoms revealed only by transesophageal atrial pacing at peak exercise. Furthermore, in this patient, transesophageal atrial pacing was also effective in the evaluation of the efficacy of propafenone therapy. The absence of induction of atrial tachyarrhythmias in the control group confirms the selectivity of transesophageal atrial pacing. Transesophageal atrial pacing at rest induced supraventricular tachycardia in 3 of 5 patients with palpitations during normal activity. In the other 2 patients, transesophageal atrial pacing at rest could not induce supraventricular tachycardia, presumably because of a long refractory period of the atria. In this study, atrial fibrillation or flutter in patients without syncope was induced in 44% at rest and in 22% during exercise, and there was no significant difference between those with rate-dependent and with stable ventricular preexcitation. Moreover, atrial fibrillation was inducible only at rest in some patients, and only during exercise in others. We believe it is necessary to examine a larger number of patients to speculate about these data, but we suspect this difference may be due to the individual adrenergic response profiles of the atrial myocardium.

In conclusion, transesophageal atrial pacing at rest and during exercise is an important diagnostic tool in the evaluation of children with ventricular preexcitation. The use of exercise in an upright position can be effective in the diagnosis of symptomatic atrial tachyarrhythmias during effort and is more physiologic than the use of sympathomimetic drugs.[18,19] Transesophageal atrial pacing should not be considered an alternative to invasive electrophysiologic studies, but can significantly enhance the noninvasive evaluation of children with tachyarrhythmias.

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Mono- Versus Double-Balloon Technique for Commissural Splitting After Percutaneous Mitral Valvotomy

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Percutaneous mitral valvotomy (PMV) using either the double-balloon or Inoue's monoballoon technique is an accepted therapeutic alternative for the treatment of selected patients with severe mitral stenosis.[1,2] Preliminary in vitro studies suggested commissural splitting as the principal mechanism of mitral valve area increase with both techniques.[3] Echocardiographic studies also have demonstrated commissural splitting after double-balloon PMV,[4] but the degree of splitting in relation to the technique used has not been previously defined.

Commissural splitting was prospectively evaluated in 136 subjects with technically adequate echocardiographic recordings from a total of 173 consecutive patients (79%) who underwent PMV at our institution from February 1989 to January 1991. Inoue's monoballoon technique was used in 100 patients (group A), and the double-balloon technique in 36 (group B). The techniques used for mono- and double-balloon PMVs have been previously described.[1,2] Commissural fusion and the degree of commissural splitting after PMV were analyzed (3.5 MHz transducer) in the parasternal short-axis view at mitral valve level by an experienced echocardiographer unaware of the results of PMV. Complete splitting of 1 commissure was defined as opening of the commissure to the mitral annulus, and incomplete splitting as partial opening of a previously fused commissure. Thus, commissural splitting was graded 0 to 2 (no commissures opened = 0, 1 partially or totally opened = 1, complete splitting of 1 and incomplete of the other = 1.5, and complete splitting of both commissures = 2). Mitral valve area was calculated by the Gorlin formula before and after the procedure. Balloon diameters were chosen according to body surface area (<1.5 m^2: 26 or 18 + 18 mm; 1.5 to 1.7 m^2: 28 or 18 + 20 mm; and >1.7 m^2: 30 or 20 + 20 mm, for mono- and double-balloon techniques, respectively). Data are presented as percentage and mean ± SD. Chi-square and Student's t tests, and analysis of variance were used when appropriate. A p value <0.05 was considered statistically significant.

Baseline clinical, echocardiographic and hemodynamic characteristics of both groups were similar (Table I), but group A patients were more symptomatic. Successful PMV (mitral valve area increase ≥50%) was achieved in 93% of group A and 97% of group B patients (p = not significant [NS]). After monoballoon PMV, mitral valve area increased from 0.90 ± 0.20 to 1.83 ± 0.43 cm^2 (p <0.0001), and mean mitral gradient decreased from 14.5 ± 5.9 to 4.9 ± 2.3 mm Hg (p <0.0001). After double-balloon PMV, mitral area increased from 0.94 ± 0.21 to 1.97 ± 0.47 cm^2 (p <0.0001), and mean mitral gradient decreased from 15.1 ± 5.1 to 5.4 ± 2.3 mm Hg (p <0.0001). No differences were found in mitral valve areas and gradients before or after PMV in the 2 groups. After PMV, 9 patients (7%) had no commissural splitting (4 for mitral leaflet rupture requiring surgery, 3 for inability to cross valve, and in 2 the balloon did not dilate the valve). Splitting of 1 commissure was achieved in 46 patients (34%) in whom the mitral valve area increased from 0.89 ± 0.21 to 1.80 ± 0.40 cm^2 (p <0.0001). Grade 1.5 commissural splitting was seen in 43 patients (32%), with an increase in mitral valve area from 0.94 ± 0.20 to 1.93 ± 0.46 cm^2 (p <0.0001). Complete splitting of both commissures occurred in 38 patients (28%), with mitral

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TABLE I Baseline Characteristics

	Group A (n = 100)	Group B (n = 36)
Age (year)	51 ± 13	49 ±14
Women/men	80/20	28/8
Functional class ≥ III	55 (55%)	12 (33%)*
Atrial fibrillation	62 (62%)	16 (44%)
Prior surgery	16 (16%)	4 (11%)
Total score	7.8 ± 1.8	8.0 ± 2.5
Calcium	1.7 ± 0.8	1.8 ± 1.0
Subvalvular disease	2.1 ± 0.7	2.2 ± 0.7
Thickening	2.3 ± 0.7	2.1 ± 0.7
Mobility	1.6 ± 0.6	2.0 ± 0.8
Gradient (mm Hg)	14 ± 6	15 ± 5
Cardiac index (L/min/m^2)	2.28 ± 0.51	2.53 ± 0.65
Mitral valve area (cm^2)	0.90 ± 0.20	0.94 ± 0.21

*p <0.025.

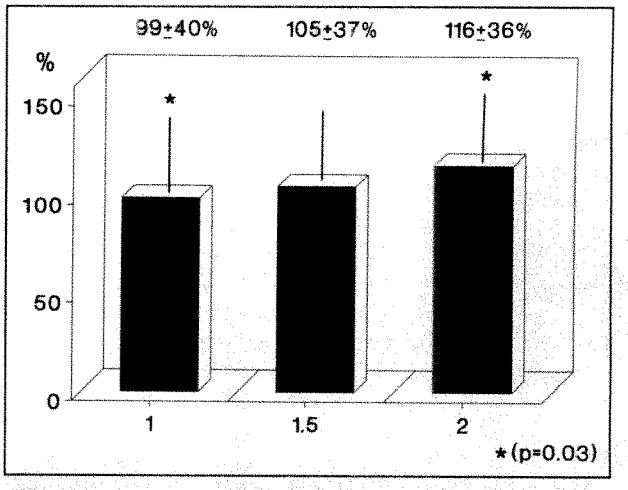


FIGURE 1. Comparison of mitral valve area increments (expressed as percentages) in patients with 1 (grade 1), 1 and part of the other (grade 1.5), and both (grade 2) commissures opened after percutaneous mitral valvotomy.

valve area increasing from 0.93 ± 0.16 to 2.02 ± 0.35 cm² (p <0.0001). Although splitting of 1 commissure was sufficient to achieve successful PMV, the increase in mitral valve area was larger in those patients with grade 1.5 commissural splitting, and even larger in those with splitting of both commissures (Figure 1). The degree of commissural splitting related to the technique used is listed in Table II. Splitting of both commissures tended to occur more frequently with the double-balloon technique, but splitting of >1 commissure was similar with both techniques (61 vs 56%, p = NS). The ratio of balloon effective dilating area to body surface area, (measured as previously described)[5] was similar in both groups and was not related to the degree of commissural splitting (Table III). The incidence of mitral regurgitation after PMV (increase >I/IV angiographic grades) was similar (9 vs 11%) in groups A and B, and again was not related to the degree of commissural splitting (4 of 46 patients [9%] with grade 1 commissural splitting, 5 of 43 [12%] with grade 1.5, and 2 of 38 [5%] with grade 2; p = NS).

TABLE II Commissural Splitting

Commissural Splitting	Group A (n = 100)	Group B (n = 36)
0	8 (8%)	1 (3%)
1	31 (31%)	15 (42%)
1.5	37 (37%)	6 (17%)*
2	24 (24%)	14 (39%)†
1.5–2	61 (61%)	20 (56%)

* p <0.05; † p <0.1.

TABLE III Balloon Effective/Dilating Body Surface Area

Commissural Splitting	Group A	Group B
1	3.99 ± 0.25	3.80 ± 0.37
1.5	4.12 ± 0.32	3.96 ± 0.40
2	3.95 ± 0.20	3.95 ± 0.37

This echocardiographic study confirms that the mechanism of mitral valve area increase after single- or double-balloon PMV is the splitting of fused commissures (as previously demonstrated in in vitro studies).[2,3] Both techniques when performed in comparable patients provided similar success rates and final mitral valve areas. Furthermore, the degree of commissural splitting obtained with both techniques was also similar, although the double-balloon technique tended to cause more frequently bicommissural splitting. This may reflect a better orientation of the 2 balloons with respect to the fused commissures during PMV. There is a limitation in the assessment of commissural splitting by 2-dimensional echocardiography (only possible in 79% of our patients), and we only used a qualitative score for commissural splitting. However, we found a good correlation between the degree of commissural splitting and the gain in mitral valve area after PMV, with the largest increments being produced when both commissures were opened. Previous reports from surgical series showed good functional results after 5-year follow-up of patients with only 1 commissure successfully opened.[6] In our experience, splitting of 1 commissure is sufficient to achieve successful dilatation of the mitral valve (99 ± 40% mitral valve area increment); however, splitting of both commissures achieves larger increments (116 ± 36%) in mitral valve area. We did not analyze whether an asymmetric pattern of commissural thickening or calcification may influence the type and degree of commissural splitting. However, it would be tempting to speculate that in patients with asymmetrical commissural thickening, the objective of PMV may be just to open the less thickened commissure in an attempt to avoid procedural related complications. Our results also demonstrate that the degree of commissural splitting is not related to the development of mitral regurgitation after PMV. Inoue's monoballoon technique (using appropriate balloon sizes) provides similar results to the double-balloon technique concerning final mitral valve areas, although there is a tendency to produce less likely complete splitting of both commissures. Longitudinal studies involving large series of patients will be necessary to elucidate the relative importance of the final mitral valve area and the degree of commissural splitting obtained with the procedure in the long-term outcome of patients undergoing PMV.

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Role of Transesophageal Echocardiography in Diagnosis of Subaortic Aneurysm

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Congenital subaortic annular aneurysm is a rare condition that has most frequently been reported among black people.[1,2] Frequently, an accurate antemortem or presurgical diagnosis cannot be made because of the peculiar anatomic location of this lesion.[1–4] Angiography may fail to show details important to the surgical approach to the patient, and transthoracic echocardiography may also miss the diagnosis.[5–7] Recently, it has been reported that transesophageal echocardiography (TEE) can define aortic annular abscesses more accurately than transthoracic echocardiography.[8] The present report summarizes our experience with subaortic aneurysm with emphasis on the role of TEE in the early diagnosis of subaortic aneurysm.

All 7 patients described in this report were evaluated at Baragwanath Hospital in Soweto, South Africa. All were black Africans. In 3 patients the aneurysms were complications of valve replacement. In 1 of these 3 patients there was infection on a native aortic valve treated with valve replacement; infection recurred on the prosthesis and was complicated by aneurysm formation (4 months postoperatively). In the other 2, the aneurysm occurred at the site of an aortic root transannular pericardial patch used to widen the aortic annulus at the time of aortic valve replacement 2 and 7 years postoperatively. In 4 patients the aneurysms were determined to be congenital because there was no predisposing surgical or infective etiology.

Each of the patients underwent biplane cardiac angiography. Left ventricular cineangiography was performed in those without an aortic prosthesis (30° right anterior oblique and 60° left oblique views). In those with an aortic prosthesis (n = 3), injection was performed in the pulmonary artery with late imaging of the levophase (anteroposterior and lateral views). Aortic root cineangiography was performed in all patients.

Transthoracic echocardiography was performed in all 7 patients, and TEE was performed in 6. All echocardiograms were performed on a Hewlett-Packard Sonos 500 or 1000 imaging system. The TEE probe was a single plane 5 MHz probe. For transthoracic echocardiography, cardiac structures were examined extensively in multiple standard and tilted parasternal long-axis views and apical 2- or 4-chamber views. For TEE, after giving informed consent, patients were given topical anesthetic spray but no pharmacologic sedation. Standard transverse views were obtained. Images were recorded on video tape for playback analysis.

Angiography demonstrated the presence of an aneurysm in all 7 patients. In 5 of 7 location of the origin was seen on the angiogram as being below the aortic valve, but in 2 patients (both postaortic valve replacement), it could not be determined whether the aneurysm arose from above or below the valve because of the presence of paravalvular leaks. In none of the angiograms could the neck of the aneurysm be clearly identified. Transthoracic echocardiography correctly localized the level of the aneurysm (subaortic) in all 4 patients in whom the etiology was congenital. However, transthoracic echocardiography failed to localize the level of the origin of the aneurysm in 2 patients (both with aortic prostheses); in another patient, also with an aortic prosthesis, the presence of the aneurysm was initially missed by transthoracic echocardiography, and only was identified in retrospect after angiography demonstrated an aneurysm. The neck of the aneurysm was clearly identified by transthoracic echocardiography in only 2 patients, both of which were congenital in origin. TEE was not used to establish the diagnosis in 2 patients. In 1 patient, the diagnosis was clear from both the angiogram and transthoracic echocardiography, including the location of the neck of the aneurysm. In the other patient, the diagnosis of subaortic aneurysm was established at surgery, but TEE demonstrated the recurrence of subaortic aneurysm postoperatively. Whenever TEE had been used (n = 6), it precisely located the neck of the aneurysm and its origin from the outflow tract. Figures 1 through 4 illustrate the potential

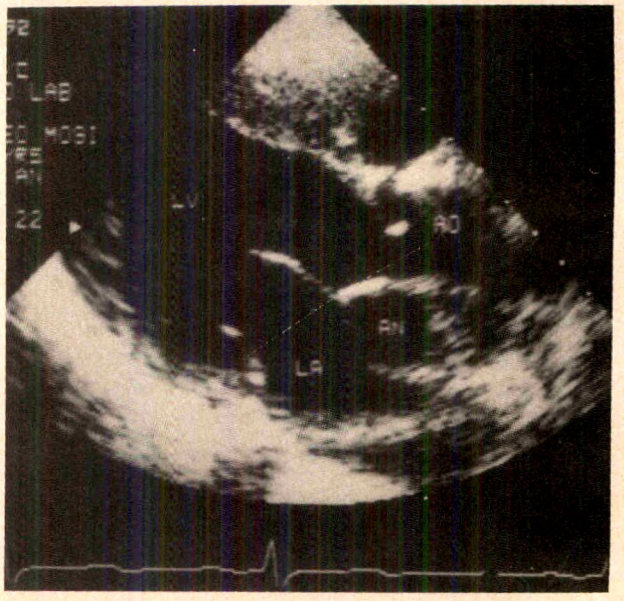


FIGURE 1. Parasternal long-axis 2-dimensional echocardiographic image showing the presence of a subaortic aneurysm (AN) partially filled with clot posterior to the aorta (AO) and compressing the left atrium (LA). The neck of the aneurysm could not be identified on the transthoracic study. LV = left ventricle.

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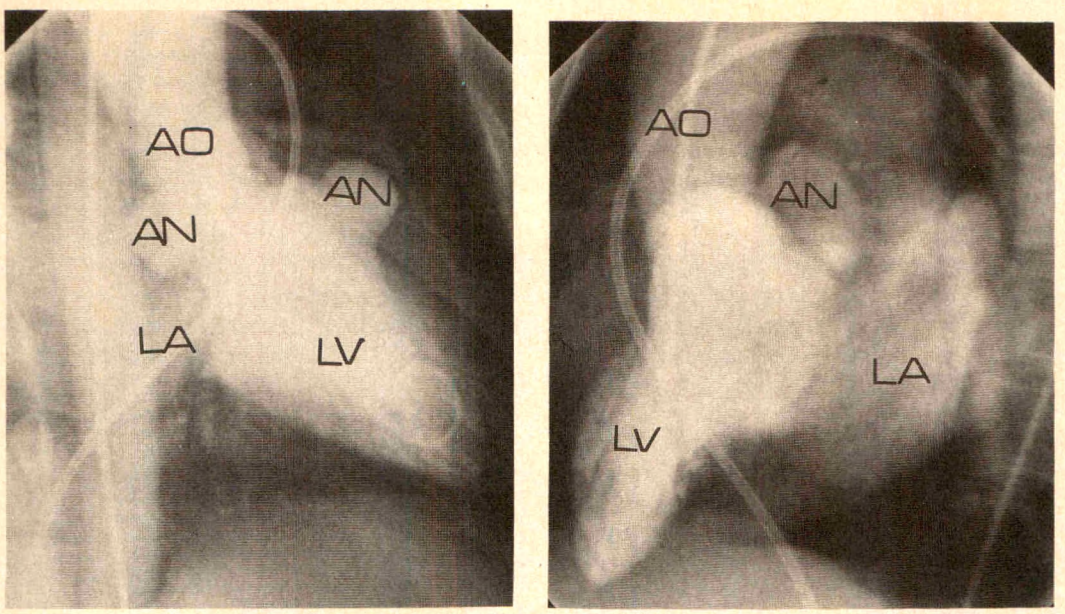


FIGURE 2. Right anterior oblique *(left)* and left anterior oblique *(right)* cineangiograms of the same patient showing the aneurysm (AN) extending anterior and posterior around the aorta (AO). The neck of the aneurysm could not be identified. LA = left atrium; LV = left ventricle.

superiority of TEE imaging in the evaluation of subaortic aneurysms.

Subaortic aneurysm is an uncommon lesion that has mainly been reported among black Africans.[1,2] However there are some reports showing it may occur as well in Europe, Haiti and in the Middle East.[3,6,7] It affects both sexes and has been reported in patients aged between 10 days and 57 years.[2,9] The etiology was originally thought to be congenital but an infective etiology has also been reported.[1,2,6] In congenital cases, the defect is thought to be a weakness in the connective tissue comprising the trigone below the valve.[1,10] Such a congenital defect may also be responsible for submitral aneurysms, which have been reported more frequently.[1,2] The presence of both congenital submitral and subaortic aneurysm has been reported in the same patient.[1,2] In this report, the lesion was presumed to be congenital in 4 patients since there was no other apparent etiology. In 1 patient the aneurysm was infective in etiology. In the other 2, the aneurysm occurred as a result of the use of a transannular pericardial patch. To our knowledge, this complication of aortic annulus widening for aortic valve replacement has not previously been reported. The neck of the aneurysm can be under any of the 3 aortic valve cusps.[4,10] In our series it

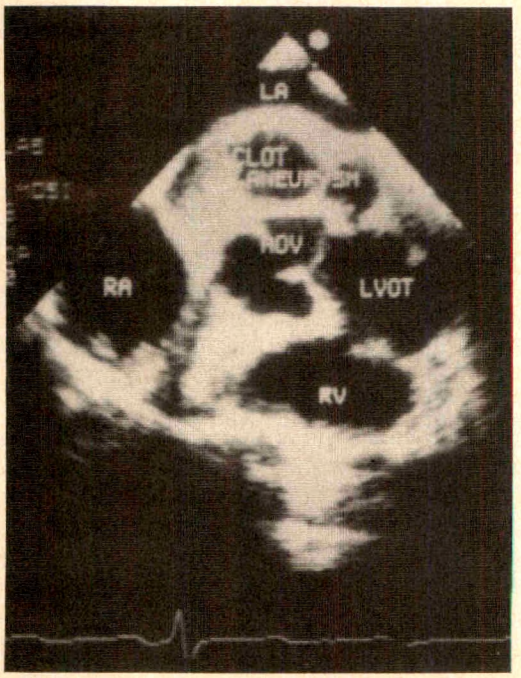


FIGURE 3. Transesophageal echocardiographic imaging of the same patient in the short-axis view clearly shows the neck of the aneurysm as arising in the left ventricular outflow tract (LVOT) below the aortic valve (AOV). The aneurysm is lobulated and is partially filled with clot. LA = left atrium; RA = right atrium; RV = right ventricle.

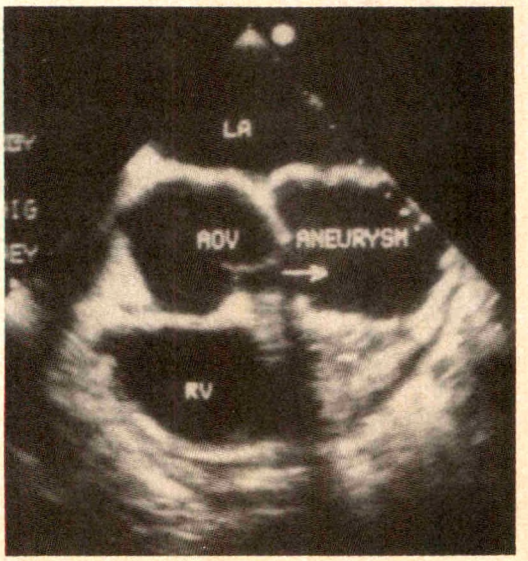


FIGURE 4. Transesophageal echocardiographic image of another patient clearly shows the neck of the aneurysm below the aortic valve (AOV) *(arrow)*. LA = left atrium; RV = right ventricle.

was under the noncoronary cusp in 6 patients and under the left cusp in 1. The aneurysm itself can be circumferential,[7] extending posteriorly[10] or anteriorly.[3] Aneurysms can produce secondary complications including sudden death due to rupture,[4] aortic incompetence (probably due to annular distortion),[3,7] and compression of other structures such as the coronary arteries[1–6] or the pulmonary artery, as reported in 1 of our patients. The diagnosis of subaortic aneurysms may be difficult because of their location and the fact that some are not associated with valve regurgitation or other clinically apparent abnormalities. In the earlier reports the diagnosis was most often made at autopsy.[1,2] In more recent reports, transthoracic echocardiography has been used to make the diagnosis, but in some cases, this procedure did not define the lesion.[4–6] The presence of an aortic prosthesis may obscure the anatomic location of the neck of the aneurysm due to echogenic scatter. In all 3 patients with aortic prostheses, transthoracic echocardiography failed to define the subaortic location of the neck of the aneurysm. Angiography may define the presence of the aneurysm, but may not identify the level of the neck of the aneurysm (i.e., whether it is annular, supravalvular or subvalvular[7]), especially where aortic incompetence or a paraprosthetic ring leak is present (contrast appears in both the left ventricle and aorta almost simultaneously). The presence of a prosthetic valve renders it difficult to perform left ventricular cineangiography. Although this limitation may be circumvented with a pulmonary injection, this also may fail to show the origin of the aneurysm. The location of the neck of the aneurysm is important in the surgical approach to the patient. Although the approach may be through an aortotomy, the surgeon should be informed if the aneurysm is below the valve where it may be more difficult to find, especially if an aortic prosthesis is present. Recently, Daniel et al[8] reported on the use of TEE in the diagnosis of periannular abscess formation in patients with aortic valve endocarditis. The diagnostic yield was better with TEE than with transthoracic echocardiography. Both the location of the neck of the aneurysm and the extent of the aneurysm were better defined with TEE than with transthoracic echocardiography. We have similarly found that TEE was superior to transthoracic echocardiography in evaluating this relatively rare lesion.

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Menopause-Induced Changes in Doppler-Derived Parameters of Aortic Flow in Healthy Women

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Currently, estrogen replacement therapy is widely used as a specific treatment for hypoestrogenic associated conditions such as vasomotor instability, genitourinary atrophy and osteoporosis. These conditions affect a substantial number of postmenopausal women.[1] The favorable effects of estrogen replacement therapy on cardiac morbidity and mortality in postmenopausal women have usually been attributed to an improved lipid profile.[2–4] It is now accepted that other mechanisms, such as the direct effect of estrogens on coronary vasculature and atherosclerotic plaque, may also have an important role in cardioprotection.[3–5] Using Doppler echocardiography we recently demonstrated a significant increase in aortic flow velocity and acceleration after 10 weeks of hormone replacement therapy.[6] These findings led us to investigate whether menopause and the related decrease in estrogen levels were associated with changes in Doppler-derived parameters of aortic flow.

Postmenopausal women referred to our menopause clinic were prospectively evaluated by Doppler echocardiography during the initial workup procedure. Menopausal state was confirmed by serum estradiol levels <10 pg/ml and follicle-stimulating hormone levels >30 mIU/ml. The study group comprised 55 healthy women without evidence of cardiovascular, pulmonary or metabolic disease who were classified in 3 groups according to the time interval since menstruation had ceased: <6 months (n = 10), 1 to 3 years (n = 29), and >5 years (n = 16). The mean ages for these 3 groups were 51, 52 and 55 years, respectively (range 47 to 55, 46 to 57, and 45 to 62, respectively; p = not significant).

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TABLE I Heart Rates, Blood Pressures, Left Ventricular Dimensions and Doppler Echocardiographic Measurements of Aortic Flow in Postmenopausal and Young Women, and in Middle-Aged Men

	Young Women (n = 15)	Postmenopausal Women				Middle-Aged Men (n = 31)
		<6 Months* (n = 10)	1–3 Years* (n = 29)	>5 Years* (n = 16)	p Value†	
Heart rate (beats/min)	67 ± 6	61 ± 6	66 ± 5	69 ± 7	NS	68 ± 8
Systolic blood pressure (mm Hg)	116 ± 9	122 ± 8	115 ± 9	126 ± 8	NS	128 ± 10
Diastolic blood pressure (mm Hg)	81 ± 7	85 ± 8	83 ± 8	77 ± 6	NS	88 ± 8
End-diastolic dimension (mm)‡	41 ± 4	42 ± 3	44 ± 4	43 ± 5	NS	44 ± 6
End-systolic dimension (mm)‡	19 ± 3	20 ± 3	21 ± 3	21 ±4	NS	20 ± 3
Peak flow velocity (cm/s)	133 ± 27	136 ± 25	119 ± 14	102 ± 17	<0.001	102 ± 9
Flow velocity integral (cm)	21 ± 3	21 ± 5	19 ± 3	16 ±4	<0.002	15 ± 2
Ejection time (ms)	310 ± 23	308 ± 27	328 ± 37	313 ± 33	NS	283 ± 13
Acceleration time (ms)	92 ± 10	99 ± 8	99 ± 8	96 ± 8	NS	95 ± 6
Mean acceleration (m/s/s)	15 ± 4	14 ± 3	12 ± 2	11 ± 2	<0.001	11 ± 1

*Since menopause onset.
†Comparing subgroups of postmenopausal women.
‡n = 12, owing to missing data.
NS = not significant.

We performed a comparison of the Doppler results in these groups with those of a group of healthy young women (mean age 32 years, range 21 to 39) with normal menstruation, and also with those of healthy middle-aged men (mean age 52 years, range 46 to 57) undergoing annual medical checkup.

Echocardiography was performed from the suprasternal notch, using a wide-angled phased array Hewlett-Packard Sonos 500 imaging system with a pulsed Doppler transducer. The following parameters were measured: peak flow velocity (midpoint of upper portion of Doppler signal at time of maximal velocity), acceleration time (time from onset of flow to peak velocity) and ejection time (time from onset until cessation of systolic flow). Flow velocity integral was internally derived by the imaging system. Mean acceleration was calculated as peak flow velocity/acceleration time. Detailed data concerning our Doppler technique and measurements were explained in a previous report from our laboratory.[7] End-diastolic and end-systolic dimensions were derived from the M-mode echocardiogram.

Analysis of variance and the Student's 2-tailed t *tests for unpaired observations were used; p values <0.05 were considered significant.*

Heart rates, blood pressures, left ventricular dimension values and Doppler measurements are listed in Table I. There was a significant gradual decrease in peak flow velocity, flow velocity integral and mean acceleration related to the time interval after the onset of menopause. There were no intergroup differences in acceleration and ejection times. Women in the immediate postmenopausal period, and younger women with normal menstruation had similar Doppler-derived parameters. The results in middle-aged men corresponded to those in women >5 years after the onset of menopause (except ejection time, which was shorter). Heart rate, blood pressure and ventricular dimensions did not reveal significant differences between the groups.

It has generally been thought that men and women of a similar age show no differences in Doppler-derived aortic flow parameters. However, flow velocity and acceleration gradually decrease with age in both sexes.[8–13] Furthermore, the findings of other investigators concerning alterations of cardiovascular hemodynamics in estrogen administration[6,14–16] led us to anticipate a possible association between an estrogen deficiency state (as in menopause) and hemodynamic changes specific to women. Based on our previous finding that hormone replacement therapy in postmenopausal women is accompanied by a significant increase in peak flow velocity, flow velocity integral and mean acceleration,[6] we concluded that menopause may be associated with the inverse changes. In fact, this study showed a gradual decrease in peak flow velocity, flow velocity integral and mean acceleration, which correlated with the time interval from onset of menopause. Furthermore, the group of women <6 months after the onset of menopause appeared to maintain the same Doppler values as those in younger women with regular menstruation. There are several explanations for these results: (1) The biological–cardiovascular effects of estrogens persist for several months after menopause despite very low plasma levels. (2) The hemodynamic changes secondary to the hypoestrogenic state develop slowly over a very long period of time. (3) During early menopause, estrogen levels may fluctuate, and the occasional increases in estrogen levels are sufficient for the maintenance of hemodynamic effects throughout that period.

Our data are important because gender differences in Doppler-derived parameters of aortic flow were not reported previously. This may have some bearing on the fact that previous studies included subjects within a relatively wide age range, and furthermore, the issue of menopause was not specifically addressed.[8–12]

Changes in Doppler-derived parameters of aortic flow may reflect not only contractility, but also variations in

heart rate, and pre- and afterloads.[17] Because heart rate, blood pressure and ventricular dimension did not reveal significant differences between our groups, the particular inotropic state of each group explains the differences in aortic flow. Furthermore, several mechanisms have been proposed to understand the direct hemodynamic effects of estrogens. Physiologically active estrogen receptors have been detected in both the heart and great vessels.[18] Estrogens may affect the activity of cardiac adrenergic and muscarinic receptors,[19] and mediate vasodilator as well as vasoconstrictor responses in the coronary arteries.[5] Myocardial lysosomal enzyme activities are influenced by estrogens.[20] Noteworthy is the study of Scheuer et al[21] on isolated rat hearts. They found that gonadectomy induced a reduction in myocardial contractile proteins and in the contractile function as measured by stroke work. These changes were reversed after estrogen replacement. Thus, their data on rats conform with our previous findings,[6] as well as our current observations on postmenopausal women. Another mechanism that we assume may explain the inotropic effect of estrogens is connected with their ability to modulate α-adrenergic receptor activity in various organs.[22-24] Because stimulation of presynaptic α-2 receptors inhibits norepinephrine release, the drugs that block α-2 receptors enhance its release. The hypothesis that estrogens reduce the responsiveness of α-2 adrenergic receptors in the heart provides a good model for our findings; whereas estrogen replacement is associated with increased inotropism, cessation of estrogen production during menopause releases inhibitory influence and restores normal function of the α-2 adrenergic activity with a concomitant decrease in norepinephrine secretion, β-adrenergic activity and myocardial contractility.

In conclusion, our study shows a consistent decrease in peak flow velocity, mean acceleration and flow velocity integral (which develops gradually in women as menopause advances), and points up the effects of estrogens on hemodynamics. Additional data are needed to clarify the precise influence of estrogens on cardiac function, and the possible cardiac effects of hormone replacement therapy in postmenopausal women.

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Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution, therefore, should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

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Heart Failure: Although acute hemodynamic studies in a small number of patients with NYHA Class II or III heart failure treated with felodipine have not demonstrated negative inotropic effects, safety in patients with heart failure has not been established. Caution therefore should be exercised when using PLENDIL in patients with heart failure or compromised ventricular function, particularly in combination with a beta blocker.

Elderly Patients or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function may have elevated plasma concentrations of felodipine and may therefore respond to lower doses of PLENDIL. These patients should have their blood pressure monitored closely during dosage adjustment of PLENDIL and should rarely require doses above 10 mg. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Peripheral Edema: Peripheral edema, generally mild and not associated with generalized fluid retention, was the most common adverse event in the clinical trials. The incidence of peripheral edema was both dose- and age-dependent. Frequency of peripheral edema ranged from about 10 percent in patients under 50 years of age taking 5 mg daily to about 30 percent in those over 60 years of age taking 20 mg daily. This adverse effect generally occurs within 2-3 weeks of the initiation of treatment.

Information for Patients: Patients should be instructed to take PLENDIL whole and not to crush or chew the tablets. They should be told that mild gingival hyperplasia (gum swelling) has been reported. Good dental hygiene decreases its incidence and severity.

NOTE: As with many other drugs, certain advice to patients being treated with PLENDIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions: ***Beta-Blocking Agents:*** A pharmacokinetic study of felodipine in conjunction with metoprolol demonstrated no significant effects on the pharmacokinetics of felodipine. The AUC and C_{max} of metoprolol, however, were increased approximately 31 and 38 percent, respectively, in controlled clinical trials, however, beta-blockers including metoprolol were concurrently administered with felodipine and were well tolerated.

Cimetidine: In healthy subjects pharmacokinetic studies showed an approximately 50 percent increase in the area under the plasma concentration time curve (AUC) as well as the C_{max} of felodipine when given concomitantly with cimetidine. It is anticipated that a clinically significant interaction may occur in some hypertensive patients. Therefore, it is recommended that low doses of PLENDIL be used when given concomitantly with cimetidine.

Digoxin: When given concomitantly with felodipine the peak plasma concentration of digoxin was significantly increased. There was, however, no significant change in the AUC of digoxin.

Other Concomitant Therapy: In healthy subjects there were no clinically significant interactions when felodipine was given concomitantly with indomethacin or spironolactone.

Interaction with Food: See CLINICAL PHARMACOLOGY, *Pharmacokinetics and Metabolism.*

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year carcinogenicity study in rats fed felodipine at doses of 77, 23.1 or 69.3 mg/kg/day (up to 28 times* the maximum recommended human dose on a mg/m² basis), a dose-related increase in the incidence of benign interstitial cell tumors of the testes (Leydig cell tumors) was observed in treated male rats. These tumors were not observed in a similar study in mice at doses up to 138.6 mg/kg/day (28* times the maximum recommended human dose on a mg/m² basis). Felodipine, at the doses employed in the two-year rat study, has been shown to lower testicular testosterone and to produce a corresponding increase in serum luteinizing hormone in rats. The Leydig cell tumor development is possibly secondary to these hormonal effects which have not been observed in man.

In this same rat study a dose-related increase in the incidence of focal squamous cell hyperplasia compared to control was observed in the esophageal groove of male and female rats in all dose groups. No other drug-related esophageal or gastric pathology was observed in the rats or with chronic administration in mice and dogs. The latter species, like man, has no anatomical structure comparable to the esophageal groove.

Felodipine was not carcinogenic when fed to mice at doses of up to 138.6 mg/kg/day (28 times* the maximum recommended human dose on a mg/m² basis) for periods of up to 80 weeks in males and 99 weeks in females.

Felodipine did not display any mutagenic activity *in vitro* in the Ames microbial mutagenicity test or in the mouse lymphoma forward mutation assay. No clastogenic potential was seen *in vivo* in the mouse micronucleus test at oral doses up to 2500 mg/kg (506 times* the maximum recommended human dose on a mg/m² basis) or *in vitro* in a human lymphocyte chromosome aberration assay.

A fertility study in which male and female rats were administered doses of 3.8, 9.6 or 26.9 mg/kg/day showed no significant effect of felodipine on reproductive performance.

Pregnancy: ***Pregnancy Category C:*** *Teratogenic Effects:* Studies in pregnant rabbits administered doses of 0.46, 1.2, 2.3 and 4.6 mg/kg/day (from 0.4 to 4 times* the maximum recommended human dose on a mg/m² basis) showed digital anomalies consisting of reduction in size and degree of ossification of the terminal phalanges in the fetuses. The frequency and severity of the changes appeared dose-related and were noted even at the lowest dose. These changes have been shown to occur with other members of the dihydropyridine class and are possibly a result of compromised uterine blood flow. Similar fetal anomalies were not observed in rats given felodipine.

In a teratology study in cynomolgus monkeys no reduction in the size of the terminal phalanges was observed but an abnormal position of the distal phalanges was noted in about 40 percent of the fetuses.

Nonteratogenic Effects: A prolongation of parturition with difficult labor and an increased frequency of fetal and early postnatal deaths were observed in rats administered doses of 9.6 mg/kg/day (4 times* the maximum human dose on a mg/m² basis) and above.

Significant enlargement of the mammary glands in excess of the normal enlargement for pregnant rabbits was found with doses greater than or equal to 1.2 mg/kg/day (equal to the maximum human dose on a mg/m² basis). This effect occurred only in pregnant rabbits and regressed during lactation. Similar changes in the mammary glands were not observed in rats or monkeys.

There are no adequate and well-controlled studies in pregnant women. If felodipine is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential hazard to the fetus, possible digital anomalies of the infant, and the potential effects of felodipine on labor and delivery, and on the mammary glands of pregnant females.

Nursing Mothers: It is not known whether this drug is secreted in human milk and because of the potential for serious adverse reactions from felodipine in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies in the United States and overseas approximately 3000 patients were treated with felodipine as either the extended release or the immediate-release formulation.

The most common clinical adverse experiences reported with PLENDIL® (Felodipine, MSD) administered as monotherapy in all settings and with all dosage forms of felodipine were peripheral edema and headache. Peripheral edema was generally mild, but it was age- and dose-related and resulted in discontinuation of therapy in about 4 percent of the enrolled patients. Discontinuation of therapy due to any clinical adverse experience occurred in about 9 percent of the patients receiving PLENDIL, principally for peripheral edema, headache, or flushing.

Adverse experiences that occurred with an incidence of 1.5 percent or greater during monotherapy with PLENDIL without regard to causality are compared to placebo in the table below.

Percent of Patients with Adverse Effects in Controlled Trials of PLENDIL as Monotherapy (incidence of discontinuations shown in parentheses)

Adverse Effect	PLENDIL % N = 730	Placebo % N = 283
Peripheral Edema	22.3 (4.2)	3.5
Headache	18.6 (2.1)	10.6
Flushing	6.4 (1.0)	1.1
Dizziness	5.8 (0.8)	3.2
Upper Respiratory Infection	5.5 (0.1)	1.1
Asthenia	4.7 (0.1)	2.8
Cough	2.9 (0.0)	0.4
Paresthesia	2.5 (0.1)	1.8
Dyspepsia	2.3 (0.0)	1.4
Chest Pain	2.1 (0.1)	1.4
Nausea	1.9 (0.8)	1.1
Muscle Cramps	1.9 (0.0)	1.1
Palpitation	1.8 (0.5)	2.5
Abdominal Pain	1.8 (0.3)	1.1
Constipation	1.6 (0.1)	1.1
Diarrhea	1.6 (0.1)	1.1
Pharyngitis	1.6 (0.0)	0.4
Rhinorrhea	1.6 (0.0)	0.0
Back Pain	1.6 (0.0)	1.1
Rash	1.5 (0.1)	1.1

*Based on patient weight of 50 kg.

In the two dose response studies using PLENDIL® (Felodipine, MSD) as monotherapy, the following table describes the incidence (percent) of adverse experiences that were dose-related.

Adverse Effect	Placebo N = 121	5.0 mg N = 72	10.0 mg N = 123	20 mg N = 50
Peripheral Edema	2.5	13.9	19.5	36.0
Palpitation	0.8	0.0	2.4	12.0
Headache	12.4	11.1	18.7	28.0
Flushing	0.0	2.8	8.1	20.0

In addition, adverse experiences that occurred in 0.5 up to 1.5 percent of patients who received PLENDIL in all controlled clinical studies (listed in order of decreasing severity within each category) and serious adverse events that occurred at a lower rate or were found during marketing experience (those lower rate events are in italics) were: *Body as a Whole:* Facial edema, warm sensation. *Cardiovascular:* Tachycardia, *myocardial infarction, hypotension, syncope, angina pectoris, arrhythmia. Digestive:* Vomiting, dry mouth, flatulence. *Hematologic: Anemia. Musculoskeletal:* Arthralgia, arm pain, knee pain, leg pain, foot pain, hip pain, myalgia. *Nervous/Psychiatric:* Depression, anxiety disorders, insomnia, irritability, nervousness, somnolence. *Respiratory:* Bronchitis, influenza, sinusitis, dyspnea, epistaxis, respiratory infection, sneezing. *Skin:* Contusion, erythema, urticaria. *Urogenital:* Decreased libido, impotence, urinary frequency, urinary urgency, dysuria.

Felodipine, as an immediate release formulation, has also been studied as monotherapy in 680 patients with hypertension in U.S. and overseas controlled clinical studies. Other adverse experiences not listed above and with an incidence of 0.5 percent or greater include: *Body as a Whole:* Fatigue; *Digestive:* Gastrointestinal pain; *Musculoskeletal:* Arthritis, local weakness, neck pain, shoulder pain, ankle pain; *Nervous/Psychiatric:* Tremor; *Respiratory:* Rhinitis; *Skin:* Hyperhidrosis, pruritus; *Special Senses:* Blurred vision, tinnitus; *Urogenital:* Nocturia.

Gingival Hyperplasia: Gingival hyperplasia, usually mild, occurred in < 0.5 percent of patients in controlled studies. This condition may be avoided or may regress with improved dental hygiene. (See PRECAUTIONS, *Information for Patients.*)

Clinical Laboratory Test Findings: ***Serum Electrolytes:*** No significant effects on serum electrolytes were observed during short- and long-term therapy (see CLINICAL PHARMACOLOGY, *Renal/Endocrine Effects*).

Serum Glucose: No significant effects on fasting serum glucose were observed in patients treated with PLENDIL in the U.S. controlled study.

Liver Enzymes: One of two episodes of elevated serum transaminases decreased once drug was discontinued in clinical studies; no follow-up was available for the other patient.

OVERDOSAGE: Oral doses of 240 mg/kg and 264 mg/kg in male and female mice, respectively, and 2390 mg/kg and 2250 mg/kg in male and female rats, respectively, caused significant lethality.

In a suicide attempt, one patient took 150 mg felodipine together with 15 tablets each of atenolol and spironolactone and 20 tablets of nitrazepam. The patient's blood pressure and heart rate were normal on admission to hospital; he subsequently recovered without significant sequelae.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly bradycardia.

If severe hypotension occurs, symptomatic treatment should be instituted. The patient should be placed supine with the legs elevated. The administration of intravenous fluids may be useful to treat hypotension due to overdosage with calcium antagonists. In case of accompanying bradycardia, atropine (0.5-1 mg) should be administered intravenously. Sympathomimetic drugs may also be given if the physician feels they are warranted.

It has not been established whether felodipine can be removed from the circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: The recommended initial dose is 5 mg once a day. Therapy should be adjusted individually according to patient response, generally at intervals of not less than two weeks. The usual dosage range is 5-10 mg once daily. The maximum recommended daily dose is 20 mg once a day. That dose in clinical trials showed an increased blood pressure response but a large increase in the rate of peripheral edema and other vasodilatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

PLENDIL should be swallowed whole and not crushed or chewed.

Use in the Elderly or Patients with Impaired Liver Function: Patients over 65 years of age or patients with impaired liver function, because they may develop higher plasma concentrations of felodipine, should have their blood pressure monitored closely during dosage adjustment (see PRECAUTIONS). In general, doses above 10 mg should not be considered in these patients.

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For more detailed information, consult your MSD Representative or see complete Prescribing Information.

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Use of Intracoronary Ultrasound to Identify the "True" Coronary Lumen in Chronic Coronary Dissection Treated with Intracoronary Stenting

Thomas E. Schryver, MD, Jeffrey J. Popma, MD, Kenneth M. Kent, MD, PhD, Martin B. Leon, MD, Sharon Eldredge, RN, and Gary S. Mintz, MD

Plaque fracture, intimal flaps and medial dissections resulting from coronary angioplasty can be readily identified using high-frequency intracoronary ultrasound.[1] Tissue and atheroma characterization using intracoronary ultrasound also may allow identification of structural abnormalities and stenoses not readily apparent using standard angiographic methods.[2,3] We report a case in which intracoronary ultrasound was used to identify the "true" coronary artery lumen in a patient with a severe coronary dissection and a double-lumen coronary 6 months after apparently successful balloon angioplasty. Correct identification of the true coronary lumen using intracoronary ultrasound allowed successful intracoronary stent placement and obliteration of the false channel.

An active 72-year-old woman developed unstable angina 7 months after an inferior wall myocardial infarction. Initial cardiac catheterization demonstrated a single, discrete 90% stenosis of the midright coronary artery. Coronary angioplasty was successfully performed, but 4 weeks later the patient developed recurrent chest pain. Subsequent catheterization revealed the recurrence of the midright coronary artery stenosis at the prior angioplasty site. The lesion was successfully redilated, although a dissection was found immediately after balloon dilatation. The patient remained symptom-free for the ensuing 6 months until recurrent angina developed. After exercise thallium scintigraphy demonstrated a reversible inferior defect, repeat catheterization revealed a 70% stenosis at the prior angioplasty site with a parallel tract dissection, creating the appearance of a double lumen within the vessel (Figure 1). Intracoronary stent placement was planned for recalcitrant restenosis, although the true coronary lumen was not readily apparent. Using an 8Fr Judkins right-4 guiding catheter, a 0.014 inch high torque floppy coronary guidewire was advanced across the lesion through the medial channel. To identify the true coronary lumen, intravascular ultrasound images (Intertherapy, Inc., Santa Ana, California) were obtained. A 25 MHz transducer-tipped catheter within a 3.9Fr monorail sheath was advanced to a position in the right coronary artery distal to the lesion; the entire catheter was rotated at 1,800 rpm and withdrawn proximally at a speed of

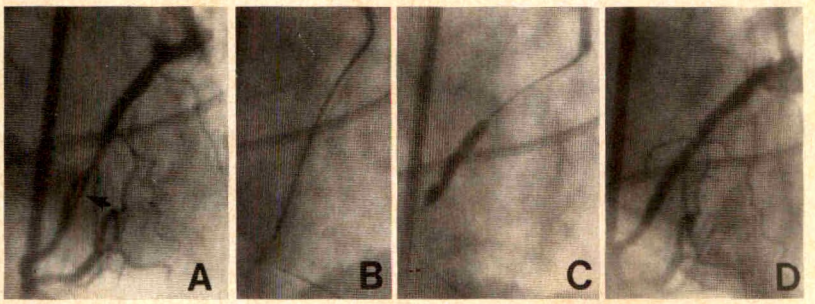


FIGURE 1. ***A,*** **angiogram of midportion of right coronary artery demonstrating "double-barrel" chronic dissection** ***(arrow).*** ***B,*** **ultrasound imaging catheter is positioned distal to lesion and withdrawn proximally.** ***C,*** **after confirmation of "true" lumen, 3.5 mm intracoronary stent is deployed, and** ***(D)*** **excellent angiographic result is obtained.**

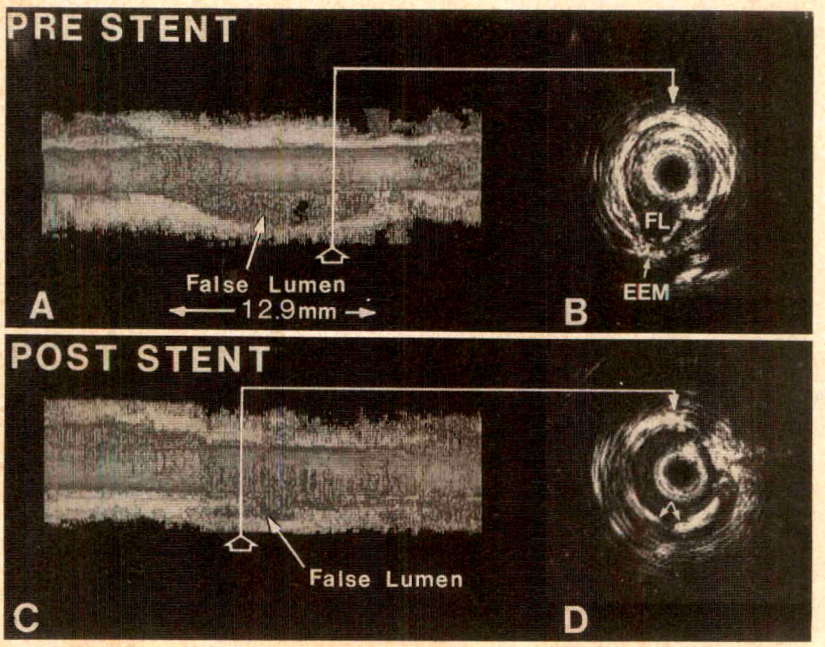


FIGURE 2. Initial 3-dimensional ***(A)*** **and 2-dimensional** ***(B)*** **ultrasound images show true lumen surrounded by plaque components continuous with proximal and distal vessels, and false lumen (FL) extending to adventitia. FL measures 12.9 mm in length.** ***C and D,*** **final intravascular ultrasound study.** ***C,*** **final 3-dimensional image shows near obliteration of FL.** ***D,*** **final 2-dimensional image shows highly reflective stent** ***(small white arrows).*** **EEM = external elastic membrane.**

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0.5 mm/s using a prototype mechanized pullback. Immediate review of these ultrasound images verified that the medial lumen was the true lumen; there was continuity of the intima and plaque components surrounding the imaging catheter in the region of the lesion (Figure 2). The dissection plane of the "false" lumen was also identified as extending through to the media and adventitia, with the false lumen adjacent to the adventitia. A computer-assisted graphics program (ImageComm, Sunnyvale, California) was used to obtain 3-dimensional image reconstruction. Importantly, the length of the dissection was measured to be 12.9 mm (suitable for stent placement).

A 3.5 mm balloon expandable tubular-slotted stent (Johnson & Johnson Interventional Systems, Warren, New Jersey) was advanced to the lesion site and its position was verified fluoroscopically. The stent balloon was then inflated to 6 atm for 45 seconds. After stent deployment, an excellent angiographic result was obtained (Figure 1). Over the 0.014 inch guidewire, the ultrasound device was then repositioned beyond the lesion, and cross-sectional images were again obtained in the region of stent deployment, demonstrating near obliteration of the false lumen.

This report describes a patient in whom a chronic coronary dissection developed after 2 prior balloon angioplasty attempts. High-frequency, intravascular ultrasound was used to identify the true coronary lumen before intracoronary stent placement. By scaffolding the disrupted intima and media, intracoronary stenting resulted in obliteration of the dissection plane, and an excellent immediate angiographic result was obtained. Off-line, computer-assisted, 3-dimensional reconstruction of the intravascular ultrasound images provided spatially accurate visualization of the arterial segment and dissection plane not possible using standard angiographic methods alone.

Two aspects of this case are noteworthy. First, angiographic visualization of the right coronary artery lesion demonstrated a "double-barrel" lumen at the site of the stenosis. The 2 lumens were of similar size, and the true lumen could not be identified using standard angiographic methods. Balloon dilatation of the false coronary lumen may have resulted in worsening of the dissection, coronary occlusion or perforation. Thus, appropriate placement of the coronary guidewire was essential for a successful outcome. Intravascular ultrasound has been used after coronary intervention to identify plaque fracture, dissection and thrombus, as well as to assess dimensional improvements and residual atheroma.[1,3,4] In this report, intracoronary ultrasound was used to identify the true coronary lumen before coronary intervention. The coronary guidewire was easily advanced into the distal right coronary artery, and its position in the true coronary lumen was confirmed by "pullback" identification of a heavily calcified intima that extended proximal and distal to the lesion surrounding the imaging catheter. The dissection plane was also identified as a disruption of the intima, which extended into the media and adventitia causing separation of tissue planes. The length of the dissection was 12.9 mm, just short enough to be covered by 1 stent. In addition to its use in identifying chronic dissection planes, intravascular ultrasound may also be useful in identifying the true coronary lumen when coronary dissections develop immediately after coronary intervention, particularly when the guidewire has been withdrawn and needs to be readvanced across the lesion.

Second, in patients with abrupt closure or severe dissections after standard balloon angioplasty, intracoronary stents have been shown useful in relieving myocardial ischemia, often obviating the need for emergency coronary bypass operation.[5] Intracoronary stents have also been used to treat recalcitrant restenosis occurring late after angioplasty,[6] but their use in treating chronic coronary dissections has been less well studied. In the present report, a chronic coronary dissection was successfully treated using a tubular-slotted stent design. After stent deployment, an excellent angiographic result was obtained. The mechanism of this angiographic improvement (i.e., the scaffolding of the intima and media, and obliteration of the false lumen and dissection plane) was demonstrated using 3-dimensional reconstruction of the intracoronary ultrasound images. With the integration of intracoronary ultrasound and the computer-assisted spatial reconstruction algorithm, immediate assessment of the degree of stent expansion is now possible. This technique may be particularly useful when arterial segments are mismatched and further balloon dilatation is needed to maximize stent expansion.

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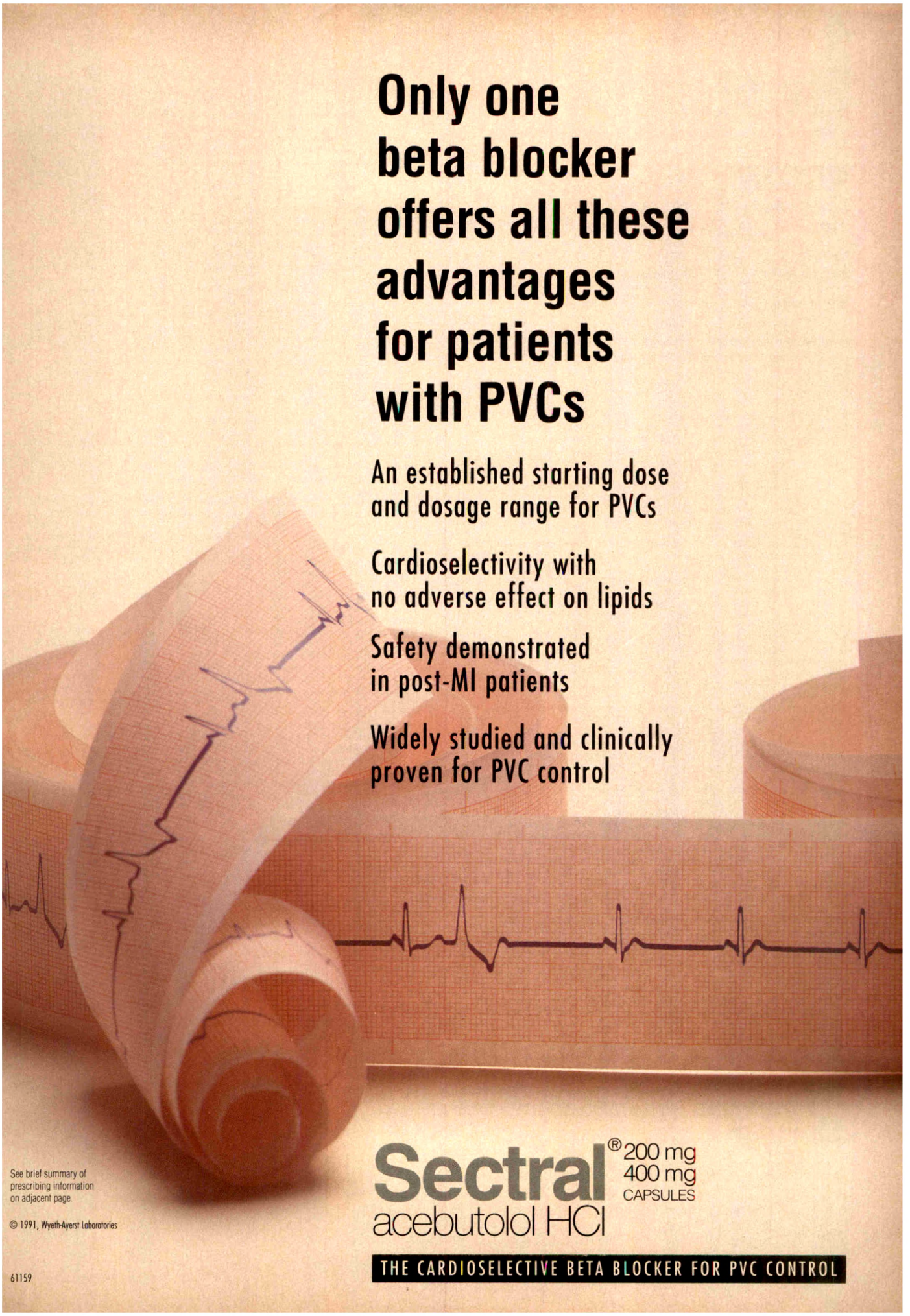
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Sectral® 200 mg 400 mg CAPSULES
acebutolol HCl

THE CARDIOSELECTIVE BETA BLOCKER FOR PVC CONTROL

Usual starting dose	**200 mg b.i.d.**
Optimal PVC response	**600 mg to 1200 mg per day**
Use in elderly	**Doses above 800 mg per day should be avoided**

(Brief Summary. See Package Circular for full prescribing information.)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N = 1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomitting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

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Ocular Deformation After Long-Term Repeated Bulbar Compression for Termination of Paroxysmal Tachycardia

Per I. Hoff, MD, Svein Faerestrand, MD, PhD, Ole-Jörgen Ohm, MD, PhD

Vagal activation attenuates atrioventricular nodal conduction properties[1,2] and may be used in patients for termination of paroxysmal reentrant supraventricular tachycardias.[3–6] We describe a patient with paroxysmal tachycardia. His method for tachycardia interruption was compression of the eyeball creating corneal deformation.

A 47-year-old male offshore operator presented to the department of ophthalmology with complaints of blurred vision; clinical examination disclosed a deformation of the left eye. He explained that since the age of 6 years he had had paroxysms of tachycardia almost daily. With the exception of a short period of treatment with digitalis he had not been on a long-term drug regimen.

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At the age of 12 his doctor recommended trying manual compression of the eyeball during tachycardia attacks. Because this method proved successful on every occasion, he did not seek further medical advice for the next 35 years. He always compressed the left eye during the procedure. During the last year before admission he recognized visual disturbance as a ring-shaped structure with multiple illuminated points when he looked at a light. He realized that his eye had been damaged and started occasionally to use the right eyeball for tachycardia termination. He was admitted for evaluation for corneal transplantation.

The ophthalmologic examination revealed an ellipsoid deformation and discontinuation in the corneal curvature on the left eye (Figure 1) with secondary visual impairment. The visual status of the right eye seemed normal and a corneal transplant was declined at this stage, but prevention of further damage seemed mandatory. His baseline surface electrocardiogram showed sinus rhythm with normal QRS complexes. During an electrophysiologic study, an atrioventricular tachycardia with a cycle length of 360 ms could repeatedly be initiated with atrial premature stimuli within an induction zone of 140 ms. The tachycardia used a concealed left-sided accessory pathway for retrograde conduction and the atrioventricular node for anterograde conduction. The tachycardia could be interrupted with atrial or ventricular premature beats and the escape intervals after termination of induced tachycardias ranged from 1,260 to 1,560 ms. When the patient performed manual compression of the left ocular bulbus, tachycardia decelerated and was interrupted in the atrioventricular node within a few seconds and with a longer escape interval ranging from 2,020 to 2,590 ms. Using the right eyeball he could also interrupt the tachycardia with 2,000 to 2,120 ms escape intervals. An attempt by one of the staff physicians to compress the eyeball could not interrupt tachycardia as a specific pressure and direction of force was necessary for proper effect.

A permanent cure seemed necessary and surgical treatment was performed on March 19, 1991. On inspection of the heart a broad area of left-sided atrioventricular connecting tissue was seen, but the intraoperative mapping during spontaneously occurring tachycardia demonstrated a single accessory pathway located in a left strict lateral position. The pathway was interrupted

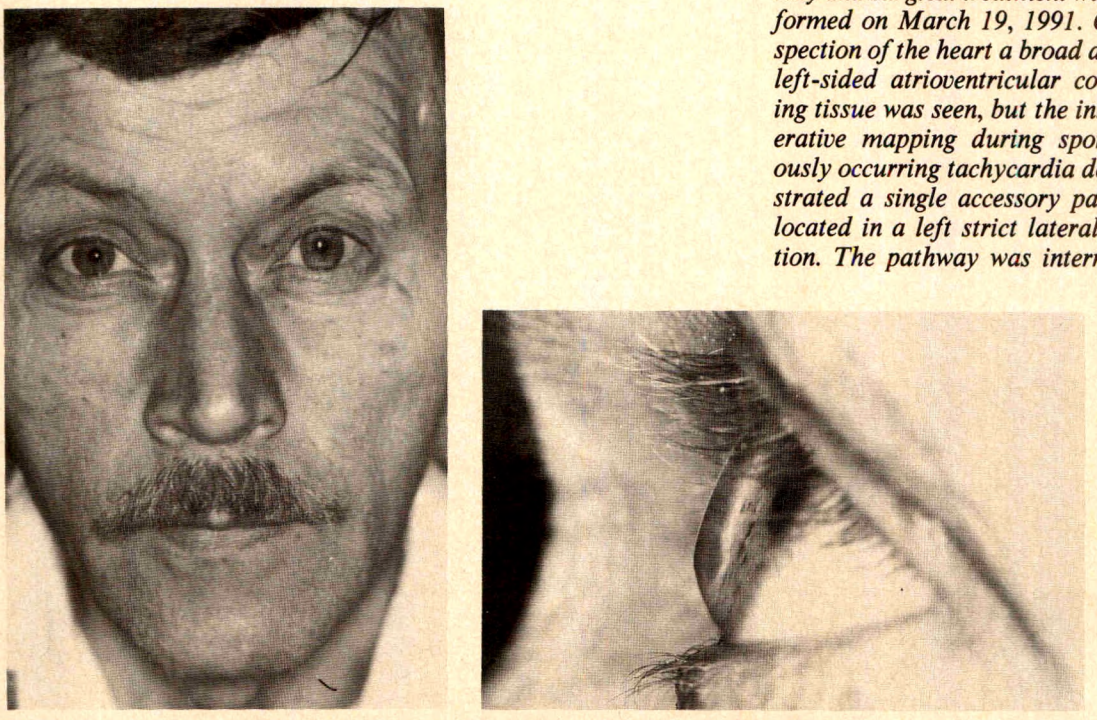


FIGURE 1. Frontal view of eyes discloses an ellipsoid deformation of the left pupil and iris *(left)*. Lateral close-up view shows an interrupted curvature of the left cornea *(right)*.

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with atrial endocardial dissection combined with cryoablation on the ventricular side of the incision. No ventriculoatrial conduction was present over the accessory pathway at repeat study 1 week later using the standard perioperatively placed atrial and ventricular pacing leads. The atrioventricular nodal conduction was normal and the postoperative course uneventful.

Paroxysmal supraventricular tachycardia based on accessory atrioventricular pathways may be lifelong. Drug treatment is often inconvenient because medication possesses limited ability to interrupt an acute attack and, thus, has to be used continuously for an indefinite period of time. Patients may be socially and occupationally incapacitated by their disease and may try vagal maneuvers for tachycardia interruption. Pressure on the eyeball is known to increase vagal tone but is rarely used as a long-term method. These procedures may seem benign but, as demonstrated in our case, one should strongly advise against the use of eyeball pressure to interrupt attacks of supraventricular tachycardias. Patients should undergo tachycardia substrate ablation with surgery or electrical methods.

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Calculation of Valve Area by the Gorlin Formula and Continuity Equation

We read with interest the article by Dumesnil and Yoganathan.[1] Of particular interest was the understanding that

$$(\overline{X^2}) \text{ is not equal to } (\overline{X})^2,$$

which is not always adhered to.[2] The authors correctly stated that

$$(\overline{Q^2}) \text{ is not equal to } (\overline{Q})^2.$$

Applying the same reasoning, equation (6) should be changed.

$$A = \sqrt{\overline{Q^2}}/50.4\sqrt{dP} \text{ or}$$

$$A = Qrms/50.4\sqrt{dP}$$

is not completely correct and should be changed to:

$$\sqrt{\overline{A^2}} = \sqrt{\overline{Q^2}}/50.4\sqrt{\overline{dP}}, \text{ or}$$

$$Arms = Qrms/50.4\sqrt{\overline{dP}}.$$

This is a very important point, because the area of the valve (functional or physiologic) is not constant, and changes with changing transvalvular flow and pressure gradient, as the authors noted. In fact, A in equations (6) and (1) is "Arms," not valve area, and thus, the authors did not calculate valve areas.

The authors describe an "alternate" way to obtain the same result of the continuity equation and get equation (7):

$$A = Qmean/50.4\sqrt{\overline{dP}},$$

where A is the (true) mean valve area. Equation (7) can be resimplified using the Bernoulli equation as follows: $dP = 3.94V^2$. Thus:

$$\sqrt{\overline{dP}} = (\sqrt{3.94V1^2} + \sqrt{3.94V2^2} +$$

$$\ldots + \sqrt{3.94Vn^2})/n = 1.98(\sqrt{V1^2}$$

$$+\sqrt{V2^2} + \ldots + \sqrt{Vn^2})/n.$$

Therefore: $\sqrt{\overline{dP}} = 1.98 \cdot \overline{V}$.

$\overline{V}$ is easily measured by Doppler echocardiography, and thus equation (7) can be simplified to allow noninvasive applications and written as:

$$Amean = Qmean/50.4 \cdot 1.98 \cdot$$

$$\overline{V} = Qmean/99.8 \cdot \overline{V},$$

where Amean and Qmean are temporal averages of areas and flows, respectively.

Using the same reasoning, equation (10) ($A = Q/44.3C \cdot dP$) should reflect instantaneous valve areas, and thus:

$$Amean = Qmean/44.3 \cdot 1.3C \cdot$$

$$\overline{\sqrt{dP}} = Qmean/44.3C \cdot 1.3 \cdot$$

$$1.98 \cdot \overline{V} = Qmean/99.99 \cdot C \cdot \overline{V},$$

thus yielding the temporal average of valve area as a function of mean flow, pressure gradient (mm Hg) and velocity (m/s).

Dawod Sharif, MD
Edward G. Abinader, MD, FRCPI
Haifa, Israel
26 November 1991

1. Dumesnil JD, Yoganathan AP. Theoretical and practical differences between the Gorlin formula and the continuity equation for calculating aortic valve areas. *Am J Cardiol* 1991;67:1268–1272.
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REPLY: We thank Drs. Sharif and Abinader for their interest and comments. "A" in equations (1) and (6) is, in fact, Arms. However, the orders of magnitude of the phasic changes in instantaneous pressure and flow are much more important than that of the phasic changes in instantaneous area, and it is assumed that Arms ≅ Amean. Theoretically, Amean can only be less than Arms, and differences between the continuity equation and the Gorlin formula could be still more important than what we reported. Resimplifying equation (7) using the Bernoulli equation is, in fact, going back to the continuity equation (equation [2]) through equation (4) and using mean values: Amean = Qmean/Vmean (100 · Vmean should be used if V is in m/s, and A and Q are in cm^2 and cm^3/s, respectively; note that in reality,

$$\sqrt{3.94} = 1.985, \text{ and } 1.985 \times$$

$$50.4 = 100.04,$$

and that 99.8 and 100.04 are, in fact, results of oversimplification, the true conversion factor being 100). Similarly, the equation Amean = Qmean/99.9 · C · Vmean is in fact equation (8) using mean values and 99.99 (i.e., 100) to convert V from m/s to cm/s. In going from equation (10) back to equation (8), Sharif and Abinader reemphasize that the coefficient 44.3 is incorrect and should be multiplied by 1.3 to account for the conversion of cm H_2O to mm Hg. We agree that the temporal average of valve area is probably best estimated by use of the continuity equation and Doppler echocardiographic measurements of flow and velocity. Note also that

$$\overline{\sqrt{dP}} \text{ does not equal } \sqrt{\overline{dP}}$$

and is not usually a readily available parameter.

Jean G. Dumesnil, MD
Sainte-Foy, Québec, Canada
Ajit P. Yoganathan
Atlanta, Georgia
15 January 1992

Percutaneous Pulmonary Balloon Valvuloplasty in Adults

We read with interest the Brief Report, "Effectiveness of Percutaneous Balloon Valvuloplasty in Adults with Pulmonary Valve Stenosis."[1] Concerning the immediate results and long-term follow-up of this procedure in adults, contrary to what the authors suggest,[2] more data are available. In 1988, Al Kasab et al[3] described 21 adults (aged 15 to 37 years) with severe congenital pulmonary valve stenosis who underwent successful percutaneous double-balloon pulmonary valvuloplasty. Satisfactory hemodynamic results were achieved acutely and maintained at 1- to 2-year follow-up. In 1989, Sievert et al[4] reported success of the procedure in 24 adults (aged 17 to 72 years) with pulmonary valve stenosis. No reste-

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nosis was observed at 3- to 12-month follow-up. Similar results were attained in a small series of 4 adults (aged 48 to 67 years) with pulmonary valve stenosis by Sherman et al[5] in 1990. All these data, as correctly concluded by the authors, support percutaneous balloon valvuloplasty as the procedure of choice in the treatment of adults with severe pulmonary valve stenosis.

Wing-Hing Chow, MB, MRCP
Tsun-Cheung Chow, MB, MRCPath
Aberdeen, Hong Kong
28 January 1992

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Correction

In the February 15, 1992 issue, on page 547 of the article, "Effects of Cardiac Transplantation on Ventilatory Response to Exercise," by Marzo et al, line 8 of the abstract and line 20 of the Methods section should read, "1.4 ± 0.6 years," not "1.4 ± 0.6 months."

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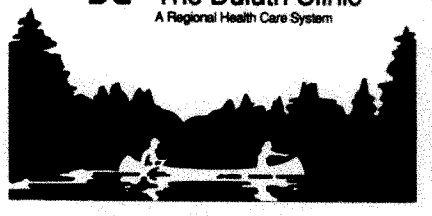
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In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values that resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m^2 basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: in vitro mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, in vitro chromosome aberration with V79 cultured lung cells, and in an in vivo cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in more than 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

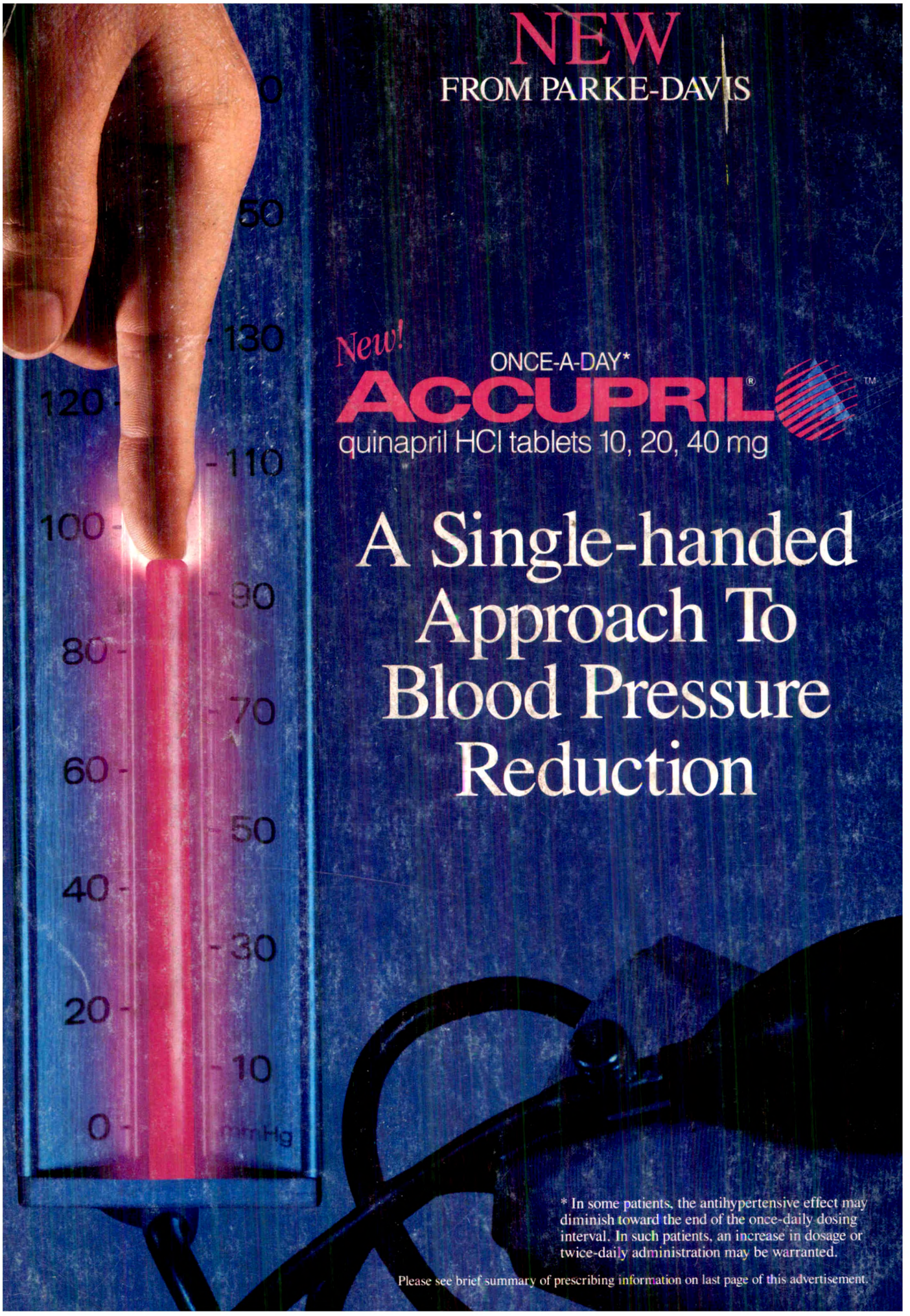
Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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The American Journal of Cardiology®

APRIL 30, 1992

A Symposium: The Role of Calcium Antagonists in Hypertension

GUEST EDITOR:

Aram V. Chobanian, MD
Dean
Boston University School of Medicine
Boston, Massachusetts

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Editor's suggestion: The symposium issues for a full year should be bound together separately from the regular issues.

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The American Journal of Cardiology

Introduction

Aram V. Chobanian, MD

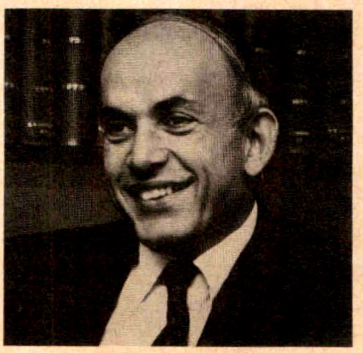
This supplement is concerned with the use of calcium antagonists in the treatment of hypertension and its cardiovascular complications. These agents have diverse actions that make them suitable for a wide spectrum of hypertensive patients. As noted in the recommendations of the Fourth Joint National Committee on the Detection, Evaluation, and Treatment of Hypertension,[1] calcium antagonists, along with diuretics, β blockers, and angiotensin-converting enzyme (ACE) inhibitors, can be considered as appropriate first-step drug therapy for hypertensive patients. They also are useful in combination with other antihypertensive medications and as treatment for hypertensive emergencies or urgencies. Further, because of the cardiac actions of calcium antagonism, these drugs may have a useful role in hypertensive patients with angina pectoris, impaired diastolic relaxation of the heart, or left ventricular hypertrophy.

The introductory article of this supplement provides a summary of the vascular effects of hypertension and the clinical sequelae of such changes. Recent data are reviewed regarding the cellular and molecular changes that develop in the arterial wall in response to hypertension. In addition, experimental data on the influence of antihypertensive drugs on the development of atherosclerosis in hypercholesterolemic animals and on the development of iatrogenic vascular lesions following balloon injury of the intima are examined. These findings provide possible new approaches to the treatment of atherosclerotic disease in humans.

The article by Katz is an excellent summary of the cardiac and vascular actions of calcium and the molecular basis for the action of calcium antagonists. As noted, calcium itself can act as an electrical messenger, which can cause membrane depolarization of both the sinoatrial and atrioventricular nodes. In the heart, the binding of calcium to troponin, a regulatory protein of the cardiac sarcomere, can cause systole. In blood vessels, calcium binding to the protein calmodulin can lead to smooth muscle contraction. Katz discusses the data on the structures of both troponin and calmodulin. Both belong to a family of calcium-binding proteins that contain helical sequences and a configuration of oxygen-containing amino acids, which provide high-affinity binding sites for calcium. Katz also characterizes the known molecular structures and amino acid sequences of the different types of calcium channels, as well as the binding sites of calcium antagonists and their effects on the calcium channels.

Weinberger summarizes data from clinical trials regarding the action of antihypertensive drugs on cardiovascular complications. He reviews the metabolic action and side effects of the different classes of antihypertensive agents and provides a rationale for the use of calcium antagonists in hypertensive patients.

Devane and colleagues summarize the characteristics of a new drug delivery system, the so-called INDAS preparation, which is used in the nife-



Aram V. Chobanian, MD

From Boston University School of Medicine, Boston, Massachusetts. Supported by NIH Grant HL 47124 (Hypertension SCOR).

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dipine-SR (sustained release) formulation. With this preparation the major absorption of nifedipine appears to occur in the large intestine. Compared with conventional therapy with nifedipine, this new formulation provides lower peak levels and less fluctuation of blood levels of nifedipine, and a much longer duration of antihypertensive effect.

White's article reviews the current status of the use of ambulatory blood pressure monitoring in the evaluation and follow-up of hypertensive patients and in the assessment of drug effects in clinical trials. He demonstrates how 24-hour blood pressure data, which typically show considerable variability in blood pressure readings, can be transformed to smooth curves by Fourier waveform analysis for comparison of treatment effects. In addition, he reports new data showing comparable blood pressure-lowering effects of nifedipine-SR and verapamil-SR.

The article by Hall provides a comprehensive review of the problem of hypertension in the elderly population. Clinical trial data, particularly on the recently completed Systolic Hypertension in the Elderly Program, are examined, and recommendations for the use of the different classes of antihypertensive drugs in the elderly are provided. In addition, the data from a study comparing the action of lisinopril with that of nifedipine-SR are reviewed.

Finally, Carr and colleagues review their findings on the blood pressure effects of nifedipine-SR. Their observations suggest good antihypertensive efficacy of the drug, with a duration of action that requires only once-daily dosing.

The reports from this symposium provide further support for the value of calcium antagonists in the treatment of hypertension. They also point out the usefulness of the INDAS drug delivery system for administering nifedipine in a manner that requires only once-daily dosing.

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Vascular Effects of Systemic Hypertension

Aram V. Chobanian, MD

Hypertension is a major risk factor for cardiovascular diseases, including coronary artery disease (CAD), stroke, left ventricular hypertrophy (LVH), congestive heart failure, peripheral vascular disease, renal failure, and aortic aneurysms. It is also a potent promoter of atherosclerosis. Observational studies have shown a linear relationship between a wide range of blood pressures and the risk for CAD and stroke. Clinical trials have indicated that hypertension reduction leads to the predicted reduction in stroke incidence, but that CAD incidence is affected to a lesser extent than predicted. The modest effect of traditional antihypertensive drugs on CAD may be due to several factors, including failure to reverse well-established coronary atherosclerosis, particularly if multiple risk factors are not reduced as well. Metabolic side effects of antihypertensive drugs or excessive lowering of blood pressure leading to inadequate myocardial perfusion, especially in patients with increased left ventricular (LV) mass, also may play important roles. Hypertension is a major cause of renal failure, particularly in black males, but control of the hypertension does not necessarily prevent deterioration of renal function. Increased glomerular pressure is thought to play a causative role in the development of renal failure in hypertensive and diabetic patients. Antihypertensive drugs may have a direct effect on the arterial wall, which may be independent of their antihypertensive action. Beta-adrenergic blockers, calcium antagonists, and angiotensin-converting enzyme (ACE) inhibitors inhibit the development of vascular lesions in response to hypercholesterolemia or to iatrogenic balloon injury, but the clinical importance of these observations remains to be determined.

(Am J Cardiol 1992;69:3E–7E)

From Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, Massachusetts. This study was supported by National Institute of Health grant HL 47124 (Hypertension SCOR).

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Elevation of systolic and/or diastolic blood pressure, even of mild degree, is a major risk factor for all important cardiovascular complications and cardiovascular mortality.[1,2] Epidemiologic studies such as the Framingham Heart Study have shown that hypertensive individuals are at much higher risk for such clinical problems as coronary artery disease (CAD), myocardial infarction, sudden death, stroke, peripheral vascular disease, and congestive heart failure (Figure 1). The risk is particularly great when elevated blood pressure is combined with other risk factors, such as hypercholesterolemia, smoking, diabetes, or left ventricular (LV) hypertrophy[3] (Figure 2).

The increased risk for both CAD and stroke appears to be progressive from low to markedly elevated blood pressure levels. Observational studies have indicated that throughout the range of diastolic blood pressures of 75–105 mm Hg, a roughly linear relation exists between blood pressure and both CAD and stroke[4] (Figure 3).

On the other hand, the results of some clinical trials have suggested that reduction of diastolic blood pressure below a certain nadir, such as 85 mm Hg, might be associated with an increase in complications of CAD.[5–7] Although the observational data indicate a small risk of cardiovascular disease in individuals with very low levels of blood pressure, the findings might not be applicable to treated hypertensive patients with CAD or LV hypertrophy who might experience adverse effects when blood pressure is reduced to a level that might jeopardize adequate myocardial perfusion.

Failure of treatment to cause large reduction in CAD also might be related to adverse metabolic effects of antihypertensive agents, e.g., diuretic-induced hypokalemia, hyperlipoproteinemia, and insulin insensitivity. However, the clinical importance of such changes is unknown. Large clinical trials are urgently needed to compare the action of different classes of antihypertensive drugs on cardiovascular complications and atherosclerosis.

A high rate of concomitant cardiovascular risk factors is present in hypertensive individuals. For example, approximately 40% of hypertensive patients have hypercholesterolemia, and 46% of hy-

percholesterolemics are hypertensive.[4] Similarly, hypertension and hypercholesterolemia are unusually common in diabetics. Control of a single risk factor, such as hypertension, may be inadequate to prevent the complications of the disease,[8] unless perhaps other risk factor abnormalities also are managed.

ARTERIAL EFFECTS OF HYPERTENSION

Hypertension typically causes major alterations in both the arterial media and intima.

Media: The most prominent change in the media is the increase in wall thickness, which counteracts the rise in wall tension associated with elevated intramural pressure. Both the total smooth muscle cell mass and the connective tissue content increase. In experimental models of chronic hypertension, medial smooth muscle cell hypertrophy is usually associated with nuclear polyploidy and increase in cellular DNA content.[9,10] Smooth muscle cell hyperplasia also has been reported in acute hypertensive models.[11] Several growth factors may be produced by the smooth muscle cells. Cell culture studies have demonstrated the gene expression of a number of growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-β, insulin growth factor, acidic and basic fibroblast growth factor, and epidermal growth factor.[12] Endogenous growth factors could be affected by hypertension and thereby modulate the growth of vascular cells by autocrine or paracrine mechanisms. We have observed that elevation in blood pressure can cause an increase in gene expression of transforming growth factor β-1 and also the cellular receptor that binds the B-chain of PDGF.[13,14] Interestingly, several vasoconstrictor agents—including epinephrine, norepinephrine, vasopressin, angiotensin II, endothelin, and serotonin—can stimulate growth of cultured smooth muscle cells, whereas vasodilator agents such as

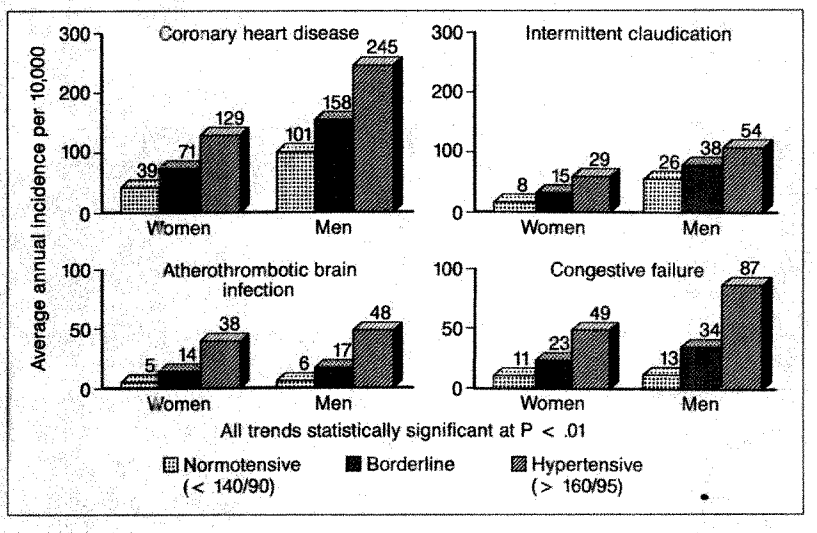


FIGURE 1. The age-adjusted risk of cardiovascular morbidity according to hypertensive status in the Framingham Heart Study. (Reprinted with permission from Epidemiology and Control of Hypertension.[1])

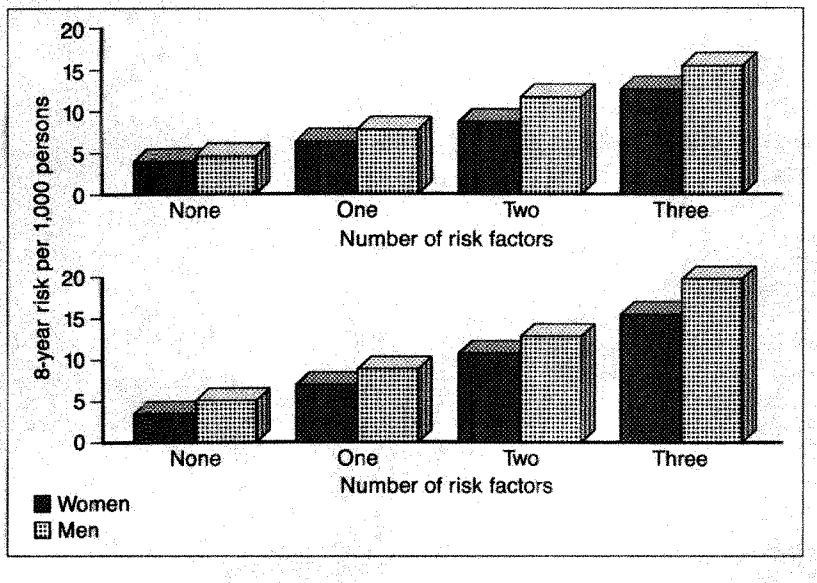


FIGURE 2. The predicted incidence of coronary heart disease among 60-year-old women (▒) and 50-year-old men (■) according to the number of risk factors. *Top.* Risk factors are defined as a total cholesterol level of 5.17–6.18 mmol/L (200–239 mg/dL), systolic blood pressure of ≥ 140 mm Hg and cigarette smoking. *Bottom.* Risk factors are defined as a total cholesterol level of ≥ 6.21 mmol/L (240 mg/dL), systolic blood pressure of ≥ 140 mm Hg and cigarette smoking. (Reprinted with permission from Working Group on Management of Patients with Hypertension and High Blood Cholesterol.[3])

endothelium-derived relaxing factor (nitric oxide) and atrial natriuretic factor may inhibit growth.[15,16] Thus, a close relation may exist between modulators of vascular tone and vascular growth.

Several connective tissue components of the arterial media, including collagen, elastin, fibronectin, and glycosaminoglycans, also are increased by hypertension.[17–19] Changes in fibronectin, which is known to be involved in wound healing and thrombosis, may play a role in cellular growth and differentiation[20] and could conceivably be one of the mediators of the smooth muscle growth induced by hypertension.

Intima: Various endothelial abnormalities are associated with hypertension. These include increase in number and change in shape of endothelial cells, increased permeability to macromolecules (including lipoproteins), and reduced endothelium-induced relaxation.[21] Circulating white blood cells adhere in increased numbers to the endothelial surface, and monocytes penetrate into the intima and accumulate there as macrophages. Smooth muscle cells of medial origin are stimulated to migrate into and accumulate in the intima. These various changes, summarized in Figure 4, appear to promote the development of atherosclerosis unless serum lipids are at low levels.

MICROVASCULATURE

Diffuse arteriolar changes are usually associated with chronic blood pressure elevation. The wall of the arteriole thickens as a result of increased numbers of smooth muscle cells[22] and connective tissue components. The greater wall thickness can lead to increased peripheral vascular resistance, as well as enhanced vascular reactivity in response to vasoconstrictive stimuli.[23] In addition, reduced perfusion of tissues may result.

Marked elevations in blood pressure, particularly of relatively sudden onset, can cause inflammation and necrosis of arterioles, leading to the clinical syndrome of malignant hypertension. The process is usually diffuse and can adversely affect the function of several organs, most notably the

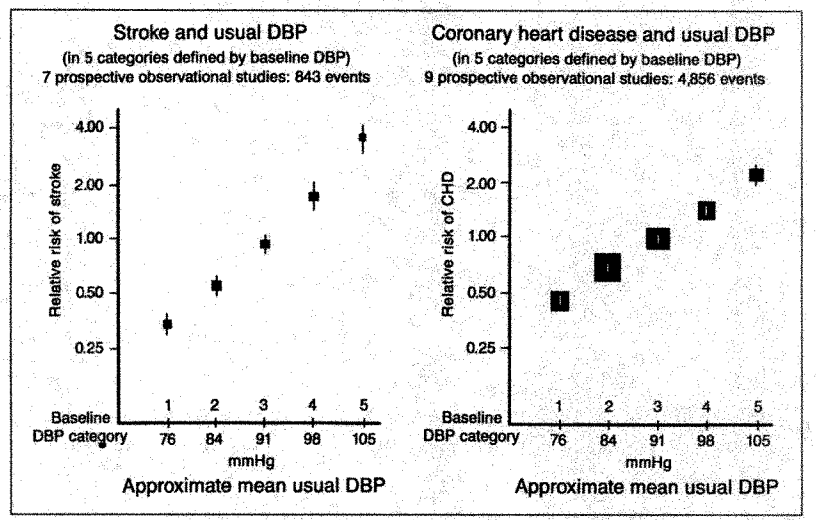


FIGURE 3. Estimates of the usual diastolic blood pressure (DBP) in each baseline DBP category are taken from mean DBP values 4 years post-baseline in the Framingham study. ■, disease risks in each category relative to risk in the whole study population; sizes of squares are proportional to number of events in each DBP category, and 95% confidence intervals for estimates of relative risk are denoted by vertical lines. CHD = Coronary artery disease. (Reprinted with permission from *Lancet*.[4])

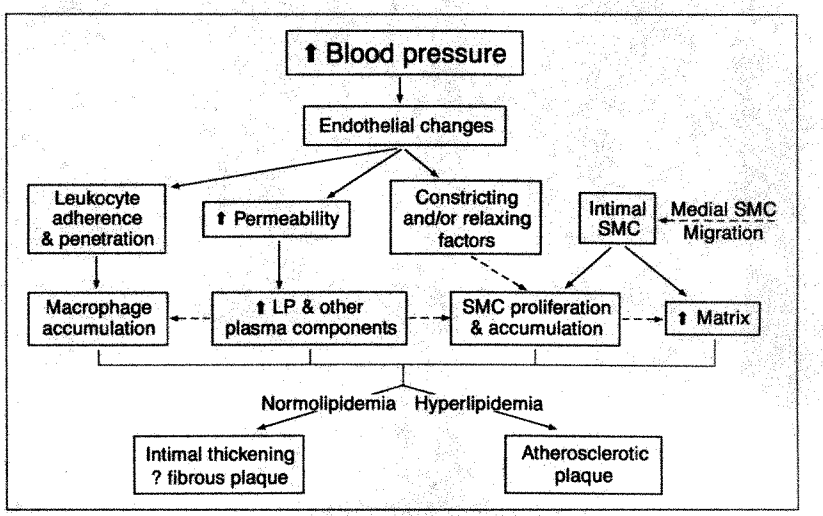


FIGURE 4. Diagram summarizing the effects of hypertension on the arterial intima. SMC = smooth muscle cell; LP = lipoprotein; ↑ = increased. (Reprinted with permission from *Hypertension*.[21])

kidney. Renal failure is the major cause of death with malignant hypertension. Cerebral edema with encephalopathy also may develop because of failure of vasoconstrictive systems that normally protect the brain from marked blood pressure elevation.

CLINICAL CONSEQUENCES OF VASCULAR CHANGES

Heart: Hypertension promotes the development of coronary atherosclerosis[24] and thereby increases the risk for myocardial infarction and sudden death. Microvascular changes in the myocardium also may play a role. Even in the absence of angiographically demonstrable CAD, hypertensive patients appear to have reduced coronary reserve in association with increased coronary vascular resistance,[25] presumably on the basis of disease of the small arteries and arterioles. Coronary microvascular changes may be particularly important in hypertensive patients with LV hypertrophy, which increases oxygen demand by the heart. Inability to meet the added demand because of small vessel disease could lead to focal ischemia and possible arrhythmias.

Kidney: In malignant hypertension, as noted above, extensive damage to small arteries and arterioles of the kidneys will occur, leading to renal failure unless early blood pressure lowering is achieved. With nonmalignant hypertension, the arteriolar sclerosis typically will involve the afferent glomerular arterioles and cause glomerular ischemia, fibrosis, and loss of nephrons. Renal failure may result in some individuals, especially black males, who appear to be particularly predisposed to developing the problem.[26]

Antihypertensive therapy does not necessarily prevent the progression of renal failure. Recent experimental studies[27] in animals have suggested that reduction of glomerular pressure by angiotensin converting enzyme (ACE) inhibitors will reduce the rate of progression of renal failure, but the clinical importance of the findings remains to be determined.

Diabetes mellitus is a common cause of hypertension and secondary renal disease. It also is a leading cause of renal failure requiring dialysis or transplantation. Strict control of both diabetes and hypertension may be needed to prevent renal failure, but the optimal therapeutic regimen remains to be determined.

Brain: Hypertension is the major cause of stroke. Atherosclerosis of the large arteries of the neck and of intracranial vessels can lead to either thrombotic or embolic stroke.[28] Small arteries and arterioles also may become involved, leading to small cerebral infarcts. These lacunar infarcts often are asymptomatic because of their small size and location. However, they can lead to specific sensory or motor disabilities.

Hypertension may induce cerebral hemorrhage by causing rupture of either large or small cerebral vessels. Many of the hemorrhages may originate from regions of aneurysmal dilation of small vessels, the so-called Charcot–Bouchard aneurysms. Experimental studies have suggested that nutritional factors, such as a high protein or potassium intake, may reduce the risk of stroke in hypertensive rats.[29,30] The mechanisms behind such protection are unknown.

Aorta: Dissecting aneurysms of the aorta are a complication of hypertension, and acute lowering of blood pressure is an important part of the therapeutic regimen for this condition. Aortic aneurysms secondary to atherosclerotic disease also are much more common in hypertensive than normotensive individuals.

EFFECTS OF ANTIHYPERTENSIVE DRUGS ON EXPERIMENTAL ATHEROSCLEROSIS

Various antihypertensive drugs, including β-adrenergic blockers, calcium antagonists, and the ACE inhibitor captopril, have been shown to diminish the development of atherosclerosis in hypercholesterolemic animals.[31–36] Calcium antagonists[37] and ACE inhibitors[38] also can reduce the size of plaques that form following balloon angioplasty. The mechanism for the vascular protective effect of these drugs is unknown, although inhibition of vascular cell growth and reduction of blood pressure and hemodynamic stresses on the arterial wall are common to all of these agents. Unlike ACE inhibitors,[35,36] calcium antagonists and β blockers have not proven effective in the Watanabe heritable hyperlipidemic rabbit with a defect in the low density lipoprotein (LDL),[39,40] but it is unknown whether the integrity of the LDL receptor is required for their action.

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Utilizing Ambulatory Blood Pressure Recordings To Evaluate Antihypertensive Drug Therapy

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Until recently, the efficacy and pharmacodynamics of antihypertensive agents were assessed by resting blood pressure measurements in the doctor's office or a research clinic. The limitations of the office or clinic blood pressure measurement include the lack of representation (from recording only 1 point of time in the dosing schedule), the effects of the doctor's office on the patient's blood pressure, and, perhaps more relevant, observer bias. Ambulatory monitoring of the blood pressure has gained worldwide acceptance as an alternative method to assess antihypertensive drug efficacy and the time–effect relation of a drug. The ambulatory monitoring devices have been refined and are smaller, more precise, and more reliable than earlier recording models. Although there are no reference standards for analysis of ambulatory blood pressure data, international consensus groups are presently addressing this problem. Key roles for ambulatory blood pressure recordings in clinical trials of antihypertensive agents now include determination of the entry criteria for patients, improving the assessment of peak/trough pharmacodynamics in the patient's own environment (including nocturnal/sleep readings), and evaluating efficacy through calculation of the hypertensive burden, or blood pressure load.

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In an editorial written approximately 4 years ago, we stated that noninvasive ambulatory blood pressure (BP) monitoring was still an uncommon method for assessing the treatment of hypertension.[1] Since that time, dozens of studies have been performed with ambulatory BP recordings, and these have demonstrated that unique information is derived from these data, especially in terms of assessing antihypertensive therapy. The key features of ambulatory BP data that enhance assessment of antihypertensive drugs fall into the following categories: lack of observer bias compared with clinic measurements, improvement in the selection process for entry into the study, ability to evaluate the pharmacodynamics of an antihypertensive drug in the patient's own environs, and the assessment of efficacy using a variety of analytic methods to determine the hypertensive burden.

This article will review the above features and put them into perspective for the assessment of antihypertensive therapy in clinical research. Background information on ambulatory BP monitoring—such as recorder precision[2–4] and relation between ambulatory BP and hypertensive target organ involvement[5–8]—has been reviewed in other comprehensive publications.

LACK OF OBSERVER BIAS WITH AMBULATORY BLOOD PRESSURE MONITORING

Recently, Bruce and colleagues[9] reported that nurse clinicians demonstrated observer bias within a short period of time following rigorous training sessions with a random zero sphygmomanometer. While the random zero sphygmomanometer avoids digit preference, it does not affect bias by a clinician performing the auscultation.

The phenomenon of observer bias is likely to be an important factor in much of the so-called "placebo response" by patients in clinical trials. In some studies of mild hypertension in which placebo is administered chronically, BP decreases by as much as 5–15 mm Hg.[10] In the recent Systolic Hypertension in the Elderly Program (SHEP)

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study, systolic pressure decreased persistently by about 12 mm Hg in the placebo group.[11] In long-term studies such as these, it is difficult to determine the role of observer bias in the creation of a placebo response. Certainly, much of the reduction of BP with placebo therapy is due to the familiarity the study patient develops with the medical care environment following several visits.

On the other hand, in short-term studies of 4–8 weeks, most patients with "white-coat" or "office" hypertension do not have a large reduction in office or clinic BP.[12–14] Thus, these patients could theoretically show a persistence of hypertensive readings in the clinic environment, despite placebo therapy. Observer bias yields the expectation of a change in BP during a double-blind therapy phase of a research trial and in a short-term study is likely to play a role in the generation of a placebo effect.[15]

In contrast to office BP measurements, ambulatory BP measurements do not appear to be affected by placebo therapy.[16–18] For example, we recently performed a double-blind study comparing the effects of a long-acting angiotensin-converting enzyme (ACE) inhibitor, cilazapril, versus placebo on casual versus ambulatory BP readings.[16] There was a nonsignificant change in 24-hour average, awake, and sleep BP readings for placebo, but all of these parameters were lowered significantly by cilazapril. In our particular study, placebo also did not cause a significant effect on clinic BP readings. In other similarly designed studies by Gould et al[17] and Dupont et al,[18] clinic BP readings significantly decreased in response to placebo, but no significant changes occurred when ambulatory pressure was measured either intraarterially or noninvasively. These findings generally support the use of ambulatory monitoring in clinical drug trials, since observer bias is effectively removed as a confounding source of BP variability.

SELECTION CRITERIA FOR TRIAL ENTRY BASED ON AMBULATORY BLOOD PRESSURE VALUES

As reported by our clinical laboratory,[12] and that of Pickering and colleagues,[13] white-coat or office hypertension is quite prevalent in the mildly hypertensive patient population (12–21%) depending on the criteria used for the diagnosis. These patients may not be appropriate candidates for participation in an antihypertensive trial, since they may show little, if any, BP response to certain agents.[19]

The first study that examined this problem was by Weber and colleagues.[20] In their study of diltiazem-SR (sustained-release), patients were chosen for study entry based on a casual, or clinic, diastolic pressure >95 mm Hg. Both casual and ambulatory BP readings were measured at the end of a placebo baseline period and following 12 weeks of double-blind therapy (placebo vs diltiazem-SR). There were no casual or ambulatory BP responses to placebo therapy. Patients with hypertension outside of the doctor's office responded significantly to diltiazem-SR monotherapy with a mean decrease in ambulatory systolic/diastolic BP of 18/13 mm Hg compared with baseline. In contrast, ambulatory BP did not decrease significantly in the white-coat hypertensive patients randomized to diltiazem-SR. Data from other studies suggest a similar lack of effect of calcium antagonists in white-coat hypertensives; much less is known about other classes of antihypertensive drugs.

The type of findings described above support the use of ambulatory BP recordings to establish entry criteria into an antihypertensive drug trial. Although this process will obviously increase the time necessary to screen patients, the population selected will include those patients who in fact require drug treatment and who will demonstrate a response to antihypertensive therapy. Furthermore, appropriate patient selection, along with the superior reproducibility of ambulatory BP recordings compared with casual pressure measurements,[21] will allow the sample size of each study group to be substantially reduced.

EVALUATING PHARMACODYNAMICS WITH AMBULATORY BLOOD PRESSURE MONITORING

Approximately 3 years ago, the Food and Drug Administration (FDA) initiated the requirement of obtaining data on trough and peak BP effects during antihypertensive drug trials. The trough BP effect is calculated from BP values obtained in the clinic at the end of the dosing interval (e.g., 12 or 24 hours). The peak BP effect represents the maximal BP-lowering effect of the study drug during a particular dosing period,[19,22] with peak BP effect being calculated as:

$$(\text{baseline } BP_{drug}) - (\text{baseline } BP_{placebo})$$

When these data are obtained from casual, resting measurements, study patients generally must spend the equivalent of the dosing period in the clinical research unit. However, use of resting BP data to assess long-term pharmacodynamic drug effects has certain limitations, e.g., BP mea-

surements in the patient's own environment during activities of daily living are unobtainable, and patients who are available for study participation over long periods of time are required. This often skews the demographics of the study population to include mostly elderly and unemployed patients.

In contrast to resting BP measurements, ambulatory BP monitoring allows the trough and peak calculations to be performed on patients within their own environment performing their normal daily activities. In addition, patients need not report to a clinic or study site in order to obtain BP measurements, and thus a wider demographic base of individuals can participate in such pharmacodynamic assessments.

An example of using ambulatory BP recordings to determine the pharmacodynamic effects of antihypertensive agents is shown in Figure 1. These data represent the findings of a randomized, double-blind, placebo-controlled, comparative trial of sustained-release nifedipine (20–100 mg once daily) versus verapamil-SR (sustained-release; 240 mg once daily to 240 mg twice daily) on ambulatory BP.[23] Study drug dosage titration occurred at 2-week intervals if the supine diastolic BP readings in the clinic were >85 mm Hg. Ambulatory BP monitoring was performed after 7 weeks of drug treatment. Of 223 patients, 70% were taking 100 mg of nifedipine-SR once daily while 77% of the patients randomized to verapamil-SR were taking 240 mg twice daily. The hourly mean BP changes from baseline post-dosing were similar for the 2 drugs, and it is evident that the antihypertensive effects were present throughout the 24 hours of BP monitoring. Using these unsmoothed curves, the peak diastolic BP response to nifedipine-SR was at 4.5 hours and for verapamil-SR peak effect was at 6 hours.

The 24-hour curves were transformed by Fourier analysis because of the variability of the unsmoothed data (Figure 1). (Fourier transforms are a type of time series analysis often used in such situations to regress the curve mathematically according to the periodicity within the data.[24,25]) The smoothed curves yielded peak-effect times of 8 hours for verapamil-SR and 9 hours for nifedipine-SR.[23] Utilizing these times, the trough and peak BP reductions (minus placebo values) were calculated and statistically compared (Figure 2). In addition, from the trough and peak diastolic BP values a ratio was calculated and, in the example shown, the ratio was 66% for once daily nifedipine-SR and 60% for once or twice daily verapamil-SR. These data illustrate that the trough effect of these drugs

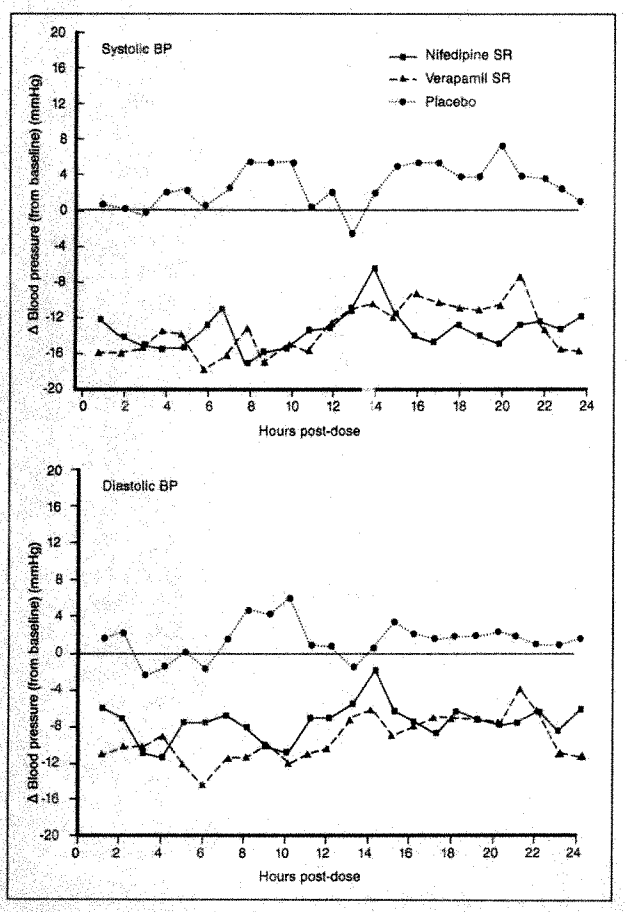


FIGURE 1. Hourly 24-hour blood pressure (BP) curves following long-term administration of placebo, nifedipine sustained-release (SR) tablets, and verapamil SR tablets in patients with mild-to-moderate hypertension. Changes in systolic (*top*) and diastolic (*bottom*) blood pressure post-dosing.

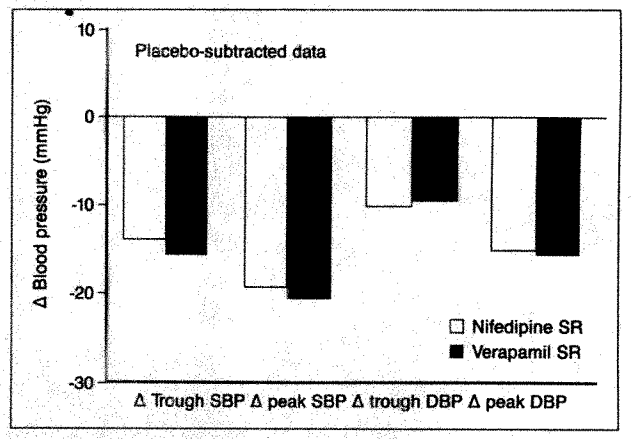


FIGURE 2. Mean reductions in the trough (12 or 24 hours following therapy, depending on dose of verapamil) and peak (8 hours for verapamil-SR and 9 hours for nifedipine-SR) ambulatory blood pressures following nifedipine-SR tablets and verapamil-SR tablets compared with placebo therapy. SBP = systolic blood pressure; DBP = diastolic blood pressure.

TABLE I Methods of Analysis of Ambulatory Blood Pressure Data

Measures of centrality
Mean and median blood pressure (for 24-hour period, awake, sleep, etc.)
Blood pressure load (percentage of elevated values)
Integrated area under the curve (using threshold values)
Visual methods and analysis of diurnal variability
Evaluation of the unsmoothed curve
Evaluation of the smoothed curve (cosinor, Fourier, spline)
Assessment according to activities and activity level
Relate blood pressure to periods of work, sleep, posture, exercise levels

is not countered by an excessive, unsafe peak effect.

METHODS OF ANALYSIS OF AMBULATORY BLOOD PRESSURE DATA TO EVALUATE EFFICACY

In addition to noted benefits of ambulatory BP recordings to assess the trough and peak hemodynamic effects of a new antihypertensive drug, this methodology is also useful to assess clinical efficacy. There is compelling evidence that ambulatory BP is superior to casual or clinic BP in predicting target organ involvement in hypertension.[6–8,14] Because ambulatory BP represents the average daily BP, many experts have advocated its use in evaluating antihypertensive efficacy. Several methods of analysis have been proposed in determining efficacy via ambulatory BP data (Table I).

The mean or median BP remains a standard parameter that can be averaged over 24 hours, while awake or asleep, or during standardized blocks of time. The 24-hour mean BP has been shown to be a stronger determinant of left ventricular hypertrophy than casual BP in several studies.[7,8,14,26] The *median* BP value may be superior from a mathematical point of view, because it is less affected by outliers than the mean BP.

"'BP load" is a simple concept that defines the proportion of BPs that are abnormal over a 24-hour period.[27] Use of the BP load is supported by data from our laboratory that related the ambulatory pressure to left ventricular structural and functional indexes.[5] In each index assessed, the correlation between BP and the cardiac changes was closer for the load than for the average BP level.

At present, it is not possible to advocate just one type of analysis to assess the ambulatory BP data in antihypertensive trials. It appears prudent to perform several complementary analyses, including visualization of the curve, calculation of the mean or median BP for periods of interest, and to analyze the area under the BP curve above threshold values[28] as an additional measurement of efficacy. Utilized together, these methods will yield the most comprehensive information about the efficacy and duration of efficacy of an antihypertensive agent.

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Calcium Antagonists for the Treatment of Systemic Hypertension

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As shown by large-scale clinical trials, the antihypertensive effectiveness of diuretics has been associated with a dramatic decrease in the incidence of stroke. This decrease, however, has not been accompanied by a similar reduction in atherosclerotic complications of hypertension, perhaps because other risk factors are important contributors to cardiovascular disease. In particular, a pathophysiologic relationship appears to exist between high blood pressure, left ventricular hypertrophy, diabetes and dyslipidemia. Thus, metabolically neutral antihypertensive agents such as calcium antagonists, which have no adverse effects on serum lipids and insulin sensitivity and can reduce left ventricular mass, are particularly suitable for the treatment of hypertension and attendant cardiovascular complications.

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According to a recent survey conducted by the National Center for Health Statistics, essential hypertension remains the most common chronic medical illness for which patients visit a physician.[1] However, the significance of elevated blood pressure derives not so much from its frequency as from its impact on cardiovascular disease. Hypertension remains a major risk factor for every form of cardiovascular disease, and particularly for stroke, myocardial infarction, congestive heart failure, and renal failure. A variety of antihypertensive drug classes are indicated for monotherapy of hypertension (Table I). An emerging body of evidence has demonstrated that the majority of conventional antihypertensive trials, typically utilizing the diuretic first, stepped-care treatment algorithm, have been associated with a dramatic reduction in the occurrence of stroke. However, the benefits in terms of reducing atherosclerotic complications such as myocardial infarction and sudden death have been inconsistent.[2]

The reasons for this disappointing failure of conventional antihypertensive therapy have been the subject of substantial debate. It is possible that conventional agents may adversely affect other risk factors contributing to cardiovascular disease. In the initial Framingham study, elevated blood pressure, as well as elevated cholesterol, diabetes mellitus, cigarette smoking, obesity, and left ventricular hypertrophy (LV) were found to be important contributing factors to cardiovascular disease.[3] The coexistence of more than one of these factors has been shown to have an additive effect on the risk for cardiovascular events.

In view of recent findings that dyslipidemic patterns are present in the majority of hypertensive patients,[4] the impact of antihypertensive treatment on these risk factors needs to be scrutinized. Similarly, it appears that insulin resistance, a precursor to frank diabetes mellitus, may be present in a large number of hypertensive subjects and may have a pathophysiologic relation to the elevated blood pressure itself.[5] Further, an increase in LV mass, as identified by echocardiography, has been

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TABLE I Antihypertensive Agents Indicated for Monotherapy

- Diuretics
- Adrenergic inhibitors
  - Adrenergic receptor blockers, α and β
  - Central adrenergic modulators
- Angiotensin-converting enzyme (ACE) inhibitors
- Calcium antagonists
- Direct vasodilators
- Drugs with combined actions
  - α- and β-adrenergic blockers
  - Diuretics and β-adrenergic blockers with vasodilator properties

TABLE II Selected Metabolic Effects of Antihypertensive Drugs by Class

Pharmacologic Class	Metabolic Effects
Diuretics	Total serum cholesterol ↑ LDL ↑ Serum triglycerides ↑ Serum glucose ↑ Abnormal glucose tolerance, glycosuria, hyperuricemia, hyponatremia, hypokalemia, hypomagnesemia
Adrenergic inhibitors	
α blockers	HDL ↑, LDL ↓ Improve insulin sensitivity
β blockers	LDL ↑, HDL ↓ Serum triglycerides ↑ Worsen insulin resistance
Angiotensin-converting enzyme (ACE) inhibitors	Hyperkalemia; improve insulin sensitivity
Calcium antagonists	Metabolically neutral No adverse effects on lipids No adverse effects on insulin sensitivity

HDL = high density lipoprotein; LDL = low density lipoprotein.

shown to be another important contributor to cardiovascular disease risk.[6] Utilizing the sensitive techniques of echocardiography, this abnormality is found to be frequently present in patients with uncomplicated hypertension.[7]

Antihypertensive drug therapy may not invariably reduce LV mass, and various antihypertensive agents have been reported to have divergent effects on this abnormality.[8] The purpose of the present report is to review the impact of conventional antihypertensive drug therapy on these risk factors with particular focus on the metabolic effects of these medications.

The various classes of antihypertensive agents have diverse metabolic effects (Table II). Thiazide diuretics have been shown to increase total cholesterol, low density lipoprotein cholesterol (LDL-C), and triglyceride levels.[9–11] Of the antisympathetic agents currently available, the metabolic effects of the α- and β-adrenergic blocking agents have been most widely studied. In general, these agents have opposite effects on lipid and glucose metabolism. Beta-adrenergic blocking drugs, with the possible exception of those agents having an intrinsic sympathomimetic action, consistently cause increases in atherogenic lipids such as triglycerides and/or LDL-C and reductions in high density lipoprotein cholesterol (HDL-C).[9] On the other hand, the peripheral α_1-adrenergic blocking drugs are the only antihypertensive agents that have been shown to have a beneficial effect on the lipid profile by reducing atherogenic lipids and/or increasing HDL-C.[12] Combination α and β blockade is generally considered to have a neutral effect on these metabolic processes. Angiotensin-converting enzyme (ACE) inhibitors appear to have no adverse effects on circulating lipids.[4] Calcium antagonists have no adverse effects on lipid components.[13,14] Further, they have been reported to have a variety of antiatherosclerotic effects.[15–17] These may be mediated by alterations in physical factors, eg, blood pressure, shear stress, which aggravates atherogenesis, and by influences on lipid metabolism and cellular uptake of atherogenic lipids. Recent studies in vascular smooth muscle cells suggest a direct antiatherogenic effect of the calcium antagonists.[18]

EFFECTS OF ANTIHYPERTENSIVE DRUGS ON CIRCULATING LIPIDS

Recent information has demonstrated that not only are atherogenic lipids important predictors of coronary artery disease (CAD), but the relation of atherogenic components—e.g., total cholesterol, the LDL to HDL ratio— may be a more sensitive index of risk for CAD.[19] Moreover, intervention studies in high-risk populations have indicated that even small changes in individual lipid components can have a dramatic effect on the risk of CAD.[20] As an example, it has been calculated that a 1% reduction in total cholesterol in patients with elevated levels of this lipid component is associated with a 2% reduction in risk for CAD.[20] Alterations to increase HDL levels appear to have an even more profound effect.

There is now abundant evidence that antihypertensive agents have significant and persistent effects on circulating lipids.

ANTIHYPERTENSIVE AGENTS AND THE DIABETIC PATIENT

At present, there is considerable interest in the role of insulin resistance in the pathogenesis and treatment of hypertension. The Framingham study, on the basis of an increase in fasting or postprandial glucose, identified diabetes mellitus as an important risk factor for most forms of cardiovascular disease.[3] More recently, an abnormal glucose

tolerance has been demonstrated in 50% of hypertensive patients, and the incidence of this abnormality has been found to be higher in treated than in either untreated hypertensives or normotensive control subjects.[21] Further, some investigators have observed fasting hyperinsulinemia in unselected and untreated hypertensive subjects.[22] The sensitive technique of the euglycemic, hyperinsulinemic clamp has revealed that, as a group, hypertensive patients are insulin resistant.[5] In addition, diuretics and β-adrenergic blocking agents worsen insulin sensitivity in hypertensive patients, whereas peripheral α_1-adrenergic blockers and the ACE inhibitor captopril have been shown to improve insulin sensitivity.[23–25] A recent retrospective report has suggested that diuretic treatment of hypertension may have an adverse effect on cardiovascular and total mortality in diabetic patients.[26] Because it was retrospective, the report was not designed to examine the comparative risks of various antihypertensive agents. Still, it adds to the evidence that diuretic treatment has deleterious effects on insulin sensitivity and glucose control.

Various experimental animal models have yielded more specific information regarding the interaction of diabetes mellitus and elevated blood pressure and its treatment. Experimentally induced diabetes mellitus in rats appears to produce changes similar to those found in diabetics. Initially, diabetes is associated with hyperfiltration and hyperperfusion of the glomerulus, which leads to mesangial hypertrophy and an increase in glomerular resistance.[27] This phase of experimental diabetic renal disease is often associated with the appearance of microproteinuria. Creatinine clearance begins to decrease from supranormal toward normal values, and as the disease progresses, glomerular filtration rate may be reduced. An increase in systemic arterial pressure is likely to occur at this time, accompanied by an increase in glomerular capillary pressure and generally a further increase in urinary protein excretion. If uncorrected, these changes lead to a progressive decline in renal function, glomerular obsolescence, and eventually renal failure.[27] In hypertensive patients with impaired renal function, the rate of progression of renal impairment seems to be responsive to antihypertensive therapy.[28] Moreover, some antihypertensive agents appear to have beneficial effects on the microalbuminuria frequently observed in diabetic hypertensive patients. Included in this group are agents such as the ACE inhibitors.[29] The impact of calcium antagonists on microalbuminuria in hypertensive diabetics is at present controversial, owing to the nature of the studies that have been reported thus far.[30] Most of the studies with calcium antagonists have been performed in small groups of patients with hypertension and diabetes (fewer than 20) and have included patients with frank nephrotic syndrome.[31] The beneficial impact of ACE inhibitors in experimental diabetic renal disease may be related to the preferential dilatation of the efferent glomerular arteriole, which reduces glomerular capillary pressure.[32] Although calcium antagonists are generally believed to have a preferential effect in dilating the afferent arteriole, and thus could be predicted to decrease glomerular capillary pressure, calcium influx is known to modulate the efferent arteriolar response to angiotensin II. Thus, calcium antagonists should have a dilatory effect on the efferent arteriole as well.[33] Future studies may further define the relative effects of various calcium antagonists on glomerular arteriolar tone. At present, inconsistent findings permit no definitive conclusions on this issue.

CARDIOVASCULAR EFFECTS OF CALCIUM ANTAGONISTS

Several antihypertensive drugs can reduce LV mass, including the antisympathetic agent methyldopa, ACE inhibitors, and calcium antagonists.[8] The α blockers have also been demonstrated to reduce regression of LV hypertrophy, but the data on the β blockers are less consistent, depending on the type, dose, and duration of β-blocker treatment.[8] Diuretics, particularly in combination with direct-acting vasodilators such as hydralazine and minoxidil, have not been consistently shown to induce regression of LV hypertrophy.

As previously mentioned, calcium antagonists can increase sodium and water excretion.[34–36] These effects have been attributed to several different actions of these drugs, the most obvious relating to the increase in renal blood flow and glomerular filtration rate associated with this class of agents. In addition, other factors may be involved in the diuretic and natriuretic effects of calcium antagonists. For example, calcium antagonists may modulate the angiotensin II-dependent sodium resorption at the renal tubular level, as they modulate the effect of angiotensin II in reducing vasoconstriction. Another potential mechanism for the diuretic and natriuretic action of calcium antagonists may be related to their ability to modulate aldosterone production at the level of the adrenal gland. The decrease in aldosterone concentration associated with calcium antagonists may reduce the stimulus for more distal sodium and water reabsorption by the kidney. These well documented natriuretic and

diuretic actions of calcium antagonists appear paradoxical, given the incidence of peripheral edema with this class of drugs. However, the edema encountered with calcium antagonists is not necessarily a reflection of sodium retention and volume expansion, but rather appears to be a hemodynamic effect at the level of the capillary. With calcium antagonists, there may be an increase in capillary pressure that induces transudation of fluid into the interstitial tissue. Thus, this edema may be best treated by mechanical means, e.g., change in position, elastic stockings, or use of a postcapillary arteriolar dilator such as a small dose of ACE inhibitor, rather than with diuretics.

CONCLUSION

Calcium antagonists are impressive antihypertensive agents, while being generally metabolically neutral, ie, devoid of adverse effects on lipids or insulin sensitivity. Calcium antagonists also have acute natriuretic and diuretic effects. Moreover, they have been reported to induce regression of LV hypertrophy and to have a variety of antiatherogenic effects.[37] Recent clinical experience suggests that calcium antagonists induce regression of coronary atherosclerosis in patients with CAD or reduce the incidence of new lesion formation, compared with either placebo or antianginal agents. Future clinical observations should provide more definitive information regarding the antiatherogenic effect of calcium antagonists.

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Molecular Basis of Calcium Channel Blockade

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Calcium plays a central role in cellular regulation, where its major function is activation. In the sinoatrial node, the entry of positively charged calcium ions through calcium channels in the plasma membrane generates an inward (depolarizing) current that contributes to pacemaker activity, whereas calcium entry in the atrioventricular (AV) node provides the major depolarizing current during AV conduction. In the working myocardial cells of the atria and ventricles, calcium entry through plasma membrane channels triggers calcium release from intracellular stores in the sarcoplasmic reticulum, and so plays a central role in excitation–contraction coupling. Calcium also serves as an intracellular messenger that binds to members of a family of intracellular calcium-binding proteins that include troponin and calmodulin. In the heart, calcium binding to troponin initiates systole, and formation of the calcium–calmodulin complex in vascular smooth muscle initiates a cascade of reactions that leads to vasoconstriction. Calcium channel blockers, by inhibiting the opening of calcium channels, attenuate all of these reactions; in the heart, they slow the sinus pacemaker and AV conduction and depress myocardial contractility. In smooth muscle, these drugs are vasodilators. Different members of the diverse group of chemical structures that block calcium channels have different specificities for different channels, and so differ in their effects on the cardiovascular system.

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Calcium represents the most important of the cellular messengers,[1] its role in signal transduction arising from 2 different characteristics of the calcium ion. The first is its ability to carry positive charge, which allows calcium entry through highly regulated membrane channels to initiate and modify membrane depolarization. In addition, calcium serves as an intracellular messenger whose appearance in the cytosol is recognized as a signal for the initiation or modification of cellular function. This latter function is brought about when calcium binds to members of a family of intracellular calcium binding proteins.

EFFECTS OF CALCIUM ON THE ELECTRICAL ACTIVITY OF THE HEART

In resting cardiac and smooth muscle, the cell interior has a negative charge; cytosolic potassium concentration is high, and sodium and calcium concentrations are low. In all regions of the heart, the downhill, passive influx of calcium contributes inward, depolarizing currents, but these currents play different functional roles in various regions of the heart.

In both the sinoatrial (SA) and atrioventricular (AV) nodes, calcium is the major ion responsible for depolarization. In the former, calcium entry plays an important role in the control of the intrinsic pacemaker activity that determines heart rate. In the AV node, where calcium currents conduct impulses from the atria to the ventricles, calcium entry is a major determinant of AV conduction, and so determines the P-R interval. In contrast, the depolarizing currents carried by calcium in the rapidly conducting cells of the His–Purkinje system and in the working myocardial fibers of the atria and ventricles are not responsible for impulse conduction. In these regions of the heart, where the upstroke of the action potential is carried by sodium ions, the major role of calcium entry is to mediate excitation–contraction coupling.

ROLE OF CALCIUM AS A "TRIGGER" IN EXCITATION–CONTRACTION COUPLING

The final signal that initiates systole in the adult heart is the binding of calcium to the regulatory

TABLE I Calcium Binding Proteins

Protein	Number of E–F Hand Regions
Common ancestor (postulated)	1
Parvalbumens	2
Intestinal calcium binding proteins	2
Troponin C	4
Myosin light chain 1	4
Myosin light chain 2	4
Myosin light chain 3	4
Calmodulin	4

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proteins of the sarcomere (see below). However, the amount of calcium that enters the cells through plasma membrane calcium channels is inadequate for this signaling function. Thus, most of the activator calcium that binds to these regulatory proteins is derived from intracellular stores in a membrane called the sarcoplasmic reticulum. As noted above, calcium release from the heart's sarcoplasmic reticulum is initiated by a small amount of calcium that enters the cell through calcium channels in specialized regions of the plasma membrane. This calcium influx represents a "trigger" that opens a special class of intracellular calcium release channels in the sarcoplasmic reticulum through a process called "calcium-triggered calcium release." This process makes available a large quantity of calcium for binding to the intracellular calcium-binding proteins that control the tension development and shortening in the working myocardial cells of the atria and ventricles.

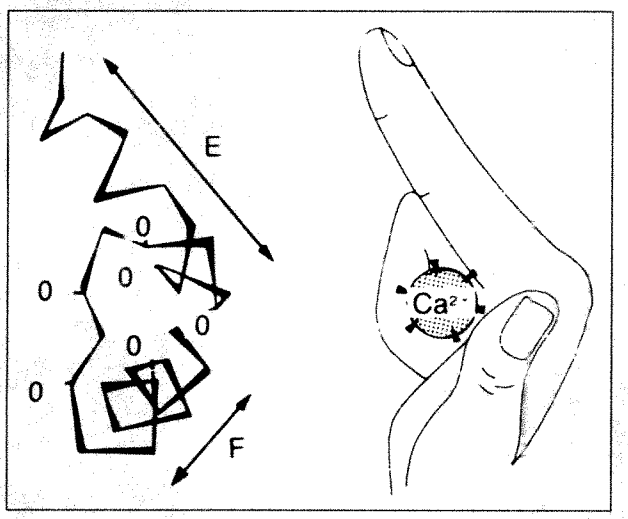


FIGURE 1. ***Left:*** **Postulated primitive calcium binding protein containing a single calcium binding site between 2 α-helical regions (E and F) in which 6 oxygen atoms (O^-) are arranged so as to coordinate tightly a calcium ion (Ca^{2+}).** ***Right:*** **Because this structure resembles a right hand, it is sometimes referred to as an "E–F hand" protein. (Reprinted with permission from Katz.[3])**

Activation of skeletal muscle also depends on calcium release from the sarcoplasmic reticulum, but the signal that opens the calcium channels in skeletal muscle is not calcium but, instead, is initiated by "voltage sensors" found in specialized regions of the plasma membrane. The voltage sensor, which moves within the membrane in response to depolarization, is related to the calcium channels as described below.

CYTOSOLIC CALCIUM BINDING PROTEINS

When calcium appears in the cytosol, its signaling function is mediated by its binding to members of a "family" of cytosolic proteins, which share a common ancestor that probably appeared some 600 million years ago.[2] This common ancestor was probably a polypeptide chain made up of 30 amino acids that contained 2 α-helical regions (designated E and F) separated by a nonhelical sequence, or loop (Figure 1). Key to the ability of these proteins to bind calcium is an arrangement of oxygen-containing amino acids at the vertices of an octahedron that forms a "pocket" in which calcium ions are coordinated with very high affinity. These oxygen-containing amino acids are concentrated in the 2 helical regions, which can be viewed as the extended index finger and thumb of a right hand in which the other folded fingers and palm correspond to the non-helical loop (Figure 1). This structure is often referred to as an "E–F hand," and proteins containing this structure as "E–F hand proteins."

The family of calcium-binding proteins includes a variety of proteins that contain 2 or 4 E–F hand regions (Table I), presumed to be derived from duplication and modification of the genes encoding the ancestral E–F hand protein. Amino acid substitutions in some of these calcium binding regions have resulted in the loss of their ability to bind calcium; in others, the specificity for calcium has been lost.

TROPONIN C, THE MEDIATOR OF EXCITATION-CONTRACTION COUPLING IN THE MYOCARDIUM

Cardiac troponin C, the calcium receptor protein of the myocardial contractile proteins, contains 4 E–F hand regions, but only 1 of these has retained the ability to bind the calcium released from the sarcoplasmic reticulum during excitation–contraction coupling. When calcium is bound to this protein, which is located along with actin in the thin filament, it causes a rearrangement of the regulatory proteins, which initiates the interactions

between actin and myosin that effect myocardial contraction.

It is of interest that another member of the family of calcium-binding proteins, a myosin light chain, rather than troponin, serves as the calcium receptor in muscle of the sea scallop. Even more fascinating is the situation in smooth muscle where, as described below, 2 different E–F hand proteins together mediate excitation–contraction coupling.

CALMODULIN, THE MEDIATOR OF EXCITATION–CONTRACTION COUPLING IN SMOOTH MUSCLE

The calcium receptor protein in smooth muscle is calmodulin, a ubiquitous intracellular calcium-binding protein that, when bound to this cation, activates protein kinases that phosphorylate a variety of cytosolic proteins. In smooth muscle, the substrate for this calcium-, calmodulin-dependent phosphorylation is yet another member of this family of proteins: a myosin light chain that, although it has lost its ability to bind calcium, still plays a key role in calcium-dependent regulation. This occurs when the calcium-, calmodulin-dependent protein kinase phosphorylates a smooth muscle myosin light chain which, in its phosphorylated form, initiates the calcium-dependent interactions between the contractile proteins of vascular smooth muscle that cause vasoconstriction.

DIVERSITY OF THE CALCIUM CHANNELS

Like the calcium-binding proteins, ion channels also are members of a diverse family of related gene products. Functional studies have demonstrated the existence of several distinct types of calcium channel. The 2 most prominent calcium channels of the heart are the T- and L-type channels (Table II). Most important is the L-type channel, which is the calcium channel whose functions were described above. The T-type calcium channel, found in nodal and specialized conducting tissue, may contribute to spontaneous pacemaker activity and the long-lasting depolarizations of the His–Purkinje system. The calcium channel blockers described in this article bind to and inhibit only the L-type channels.

STRUCTURE OF PLASMALEMMAL ION CHANNELS

In the past few years, the complete amino acid sequences of several plasmalemmal ion channel proteins have been elucidated (Figure 2). The channels are glycosylated membrane proteins made up of several peptides (Table III). Most important

TABLE II Major Calcium Channels in the Heart

Property	L-Type Calcium Channel	T-Type Calcium Channel
Threshold	Low (−40 mV)	High (−70 mV)
Inactivation	Slow (L = long-lasting)	Fast (T = transient)
Response to β-adrenergic stimulation	Stimulated	None
Response to calcium channel blockers	Blocked	None
Size	Large (15–25 pS)	Small (7–9 pS)
Found in	All cardiac cells	Conducting and nodal cells

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are the large, tetrameric α- and α_1-channel peptides of the sodium and calcium channels, respectively. These contain 4 similar subunits that surround the water-filled pore through which the ions cross the phospholipid bilayer. The corresponding structure of the potassium channel is probably a tetramer of similar subunits that are not covalently

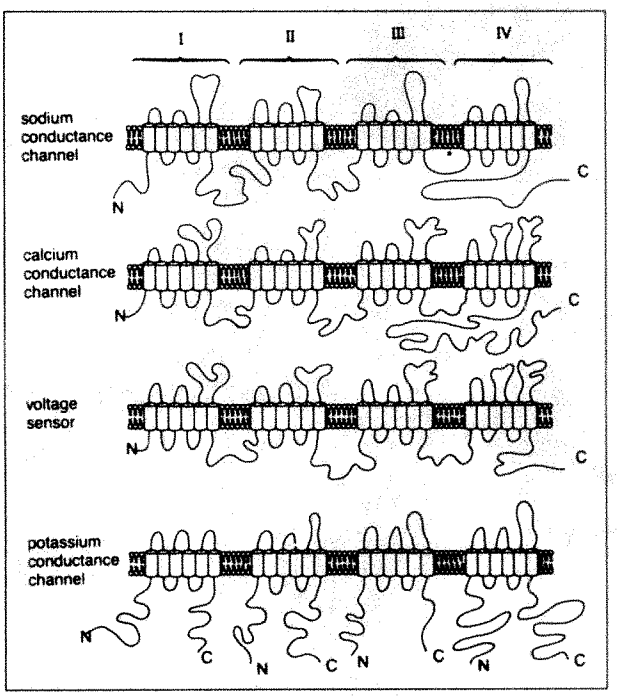


FIGURE 2. Depictions of various plasma membrane ion channels. The sodium and calcium conductance channels are tetramers made up of 4 subunits, numbered I–IV. Each subunit contains 6 membrane-spanning α-helices, S_1–S_6. The S_4 helix is believed to be the activation gate that opens the channel when the membrane is depolarized, and the cytoplasmic loop linking subunits III and IV in the sodium channel (*) is likely to represent the inactivation gate. The voltage sensor that mediates excitation–contraction coupling in skeletal muscle appears to be a proteolytic product derived from the calcium conductance channel that has lost a large portion of its C-terminal amino acid sequence. The potassium conductance channel is also made up of 4 subunits, but in this channel these are not linked to each other through a continuous peptide chain. (Reprinted with permission from Katz,[3] modified from Catterall.[4])

TABLE III Peptide Components of Voltage-Dependent Ion Channels

Ion Selectivity	Subunit	Number	Approximate Molecular Mass (Daltons)	Possible Function
Sodium	α	1	260,000	Pore, PK-A* substrate
	β	0–2	30,000–40,000	
Calcium	$\alpha_{1,212}$	1	212,000	Pore, PK-A substrate
	$\alpha_{1,175}$	1	175,000	"Voltage sensor"
	α_2	1	140,000	PK-A substrate
	β	1	54,000	PK-A substrate
	γ	1	30,000	
	δ	1	27,000	
Potassium		4	70,000–80,000	Pore

*PK-A = cyclic adenosine monophosphate-dependent protein kinase.
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linked (Table III), so that the major peptides of the different channels all contain 4 channel subunits, as depicted in Figure 2. The larger channel proteins listed in Table III are referred to as *channel peptides*, and the 4 covalently linked components of the α- and α_1-peptides of the sodium and calcium channel, numbered I–IV, are *channel subunits*. These subunits, which are similar to the corresponding free subunits of the potassium channel, all contain six *membrane-spanning α-helices,* designated S_1–S_6.

The evolution of the ion channel peptides is remarkably similar to that proposed for the calcium-binding proteins described before. Both are members of a family of multimeric proteins that have evolved from a primitive monomeric ancestor, which in the case of the ion channels is the channel subunit. Reduplication of the genes that encode the channel subunits, as for the E–F hand proteins, has given rise to the 4 covalently linked channel subunits in the large α- and α_1-peptides of the sodium and calcium channels. The functional potassium channel is also a tetramer of the channel subunits, but in this highly variable channel the subunits are not covalently linked. For this reason, potassium channels appear to be the more primitive of these structures: they are the smallest and, like the ancestral E–F hand protein (Table I), do not exhibit evidence for gene reduplication.

Potassium channels, along with the calcium channels that probably evolved next, are present in such simple organisms as protozoa, coelenterates, and ctenophores. The most recent addition to this family appears to be the sodium channels, which generate the largest and most rapidly rising action potentials that conduct far more rapidly than calcium-dependent action potentials. Since the sodium channels provide for the fastest conduction, it is not surprising that they have been found mainly in multicellular organisms[5] that require speedy communication between different regions of their bodies.

CHANNEL SUBUNIT STRUCTURE

The channel subunits are made up of six putative membrane-spanning helices.[3] Two, S_5 and S_6, are hydrophobic and so are likely to interact with the hydrophobic core of the bilayer in which the channel is imbedded. The S_1 and S_3 membrane-spanning helices, which contain negatively charged amino acids, and the S_2 helix, which contains both positively and negatively charged amino acids, probably surround the water-filled pore. Most interesting is S_4, which contains a "ribbon" of positively charged arginine and lysine residues, and which has the properties expected of the voltage sensor that opens the channel by moving within the bilayer in response to changing transmembrane potential. For this reason, the S_4 membrane-spanning helix is postulated to represent the *activation gate* whose movement in the membrane opens the channel. A likely candidate for the *inactivation gate,* which is responsible for the refractoriness that follows the transition of the channel from the open to the closed state, has also been identified (Figure 2); this is the cytoplasmic loop connecting the S_6 membrane spanning helix of subunit III and the S_1 membrane spanning helix of subunit IV.

STRUCTURE OF THE CARDIOVASCULAR CALCIUM CHANNELS

The large α_1-peptides of the calcium channels bind to all three classes of approved calcium channel blockers: dihydropyridines, benzothiazepines, and phenylalkylamines. Two forms of this α_1-peptide are found in muscle.[6] A larger, 212,000 Dalton (Da) molecule is found in the cardiac conductance channels that carry the depolarizing calcium currents described above. This peptide, in addition to binding the calcium channel blockers, is the substrate for cyclic adenosine monophosphate (cAMP)-dependent protein kinase-catalyzed phosphorylation that mediates the β-adrenergic stimulus to increase channel opening. A smaller version of the α_1-peptide, which is similar to the 212,000 Da peptide except that it lacks 320 amino acids at the C-terminal end and so has a lower molecular mass of about 175,000 Da, appears to be the structure that opens the intracellular calcium release channels in skeletal muscle sarcoplasmic reticulum when the muscle is depolarized.

Less well understood are the many smaller peptides that are associated with, and appear to regulate, many of these channels (Table III). Not

all of these small peptides are associated with the many channels found in nature; for example, functional sodium channels may contain 0, 1, or 2 β-peptides. Many of the smaller peptides associated with the calcium channel appear to play a role in channel regulation. Thus, the β-peptide, like the α_2-peptide, is a substrate for cAMP-dependent protein kinase that, when phosphorylated, activates the channel.[7,8] The δ-peptide, which is encoded by the same gene as the α_2-peptide, is linked to the latter by disulfide bonds, which suggests that, like insulin and several other proteins that are derived from "proproteins," the δ-peptide may be produced from a larger peptide by proteolysis during post-translational processing.[9] Yet another level of regulation is probably reflected in the ability of most of these peptides to be modified by post-translational glycosylation.

STATES OF AN ION CHANNEL

Studies of single channels have added greatly to our understanding of channel function and its regulation of channel function by both neurotransmitters and drugs. For example, the slow appearance of cardiac calcium currents after the membrane is depolarized (lower tracing in Figure 3) tells us little about the rates of channel openings, which are actually very rapid (middle tracing). Changes in the magnitude and time course of ionic currents are, in fact, generally due to changes in the *probability* that the channel will be found in an open state. An increase in an ionic current can occur if the channels begin their openings sooner after the stimulus, open more frequently, or continue to open for a longer period before they are inactivated.

Changes in the probability of channel opening are of considerable importance in terms of both physiologic and pharmacologic regulation. Thus, phosphorylation of the calcium channel by cAMP-dependent protein kinase, which plays a central role in the response to exercise, promotes calcium entry not by increasing the rate of channel opening or the current that it carries when open, but instead by increasing the probability that the channel will be in an open state after the membrane is depolarized.

The earlier concept that voltage-sensitive ion channels could exist in 3 functional states—open, closed (resting), and closed (inactivated) (see above)—has recently been modified on the basis of analyses of single channel recordings. These studies have shown, for example, that the dihydropyridines can both activate and inhibit calcium channel opening; in fact, some of the calcium channel blockers can do both, and at the same time! These puzzling responses are now known to reflect the ability of the drugs to modify differently the transitions among 3 states of the calcium channel.[10] Starting from the closed state, calcium channels can flicker in 2 open states: brief openings and long-lasting openings. Since these 2 open states also occur spontaneously in the absence of drugs,[11,12] these 2 modes of opening are clearly natural states of the channels. The effects of the calcium channel blockers are therefore to modify the probability that the channels will be in one or another of these states, rather than simply to "plug" the channels.

Another recently discovered property of single channels is their ability to exist in open states that differ not in their duration but in the amplitude of the current they allow to cross the membrane.[13,14] These different conductance states may arise from graded interactions among the channel subunits depicted in Figure 2. Although different conductance states of a single channel have, so far, been identified only in intracellular calcium release channels,[13,14] varying current flux through different conductance states of open plasma membrane channels could provide yet another means for regulating membrane voltage.

The transitions between opening modes and conductance states provide an elaborate means for the control of ion currents. In the case of the calcium channels of the cardiovascular system, the

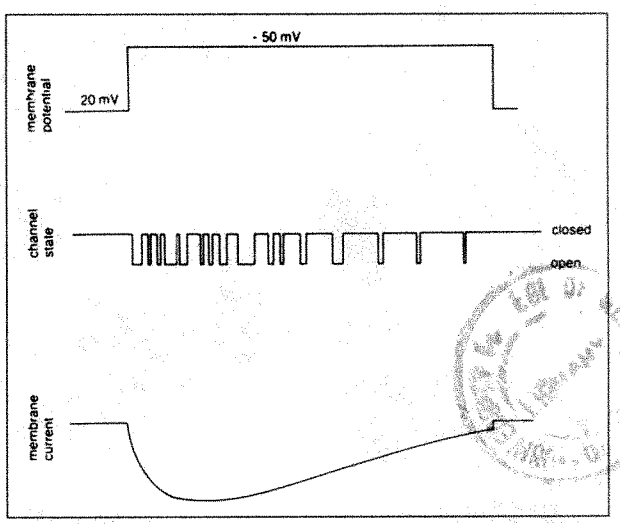


FIGURE 3. Response of a single calcium channel to membrane depolarization. Depolarization of the membrane from −20 to +50 mV (*upper tracing*) causes the channel to alternate between its closed and open states (*middle tracing*). Later, if depolarization is continued, the channel tends to open less frequently so that membrane current (*lower tracing*), after its initial increase (downward deflection), begins to fall even though membrane potential remains the same. (Reprinted with permission from Katz.[3])

ability of drugs to modify these transitions is of considerable importance in modifying the function of both the heart and vascular system. Future studies to define compounds with enhanced specificity for one or another class of calcium channels offer considerable promise for improving the therapy of cardiovascular disease.

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New Developments In Sustained-Release Antihypertensive Therapy: Formulation and Pharmacokinetic Considerations

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In order to achieve a consistently absorbed form of nifedipine over 24 hours, a novel formulation approach, INDAS, was used to develop a once-daily, sustained-release (SR) form of nifedipine that could provide effective control of blood pressure at a low total daily dose. The pharmacokinetic characteristics of this new formulation of nifedipine-SR were compared with those of divided doses of conventional nifedipine. The SR formulation was shown to achieve a lower peak plasma nifedipine level but with a prolonged plasma profile characterized by an extended time to peak plasma levels (T_{max}), a higher trough plasma level, a longer apparent half-life, and a markedly lower peak-to-trough fluctuation in plasma nifedipine concentrations. In a separate study, the gastrointestinal transit parameters and physical characteristics of the SR tablet were evaluated. This study established that the large intestine is the major site of residence and absorption for this dosage form. The physical erosion and disintegration characteristics of the SR formulation are such that a well-maintained absorption of nifedipine is consistently achieved over the 24 hour dosing interval.

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Nifedipine is a calcium antagonist commonly used in the treatment of hypertension.[1] In its conventional immediate-release capsule form, nifedipine is normally dosed 3 times daily. Such frequent daily administration may adversely affect patient compliance and hence impact on therapeutic effectiveness.[2] In addition, because of rapid absorption from the gastrointestinal (GI) tract and short elimination half-life ($t_{1/2}$ = 2 hours), the plasma nifedipine levels fluctuate markedly following administration of the conventional capsule form of nifedipine. The resultant high peak plasma nifedipine levels may be associated with some of the characteristically common adverse effects of nifedipine: increased heart rate, flushing, and headache.[3] Taking these considerations into account along with the established relation between plasma nifedipine concentration and blood pressure reduction,[4] the development of a low-dose sustained release (SR) form of nifedipine designed for once-daily administration through the achievement of prolonged therapeutically effective blood levels over 24 hours is justified. Additionally, it has been shown that slow infusions of nifedipine result in little change in heart rate in contrast to a rapid infusion, which has shown marked increases in heart rate; both regimens showed equivalent blood pressure lowering effects.[4] These data further support the potential benefits of a slow nifedipine input rate, as can be achieved through a SR formulation compared with the effects of intermittent boluses of conventional nifedipine capsules.

The formulation of nifedipine into a SR preparation that achieves consistently prolonged plasma nifedipine concentrations over the 24-hour dosing interval is technically difficult. The primary impediment lies in the extremely poor aqueous solubility of the usual crystalline form of nifedipine, which impacts on the dissolution and absorption characteristics of the drug, particularly in the final segments of the GI tract where the majority of the

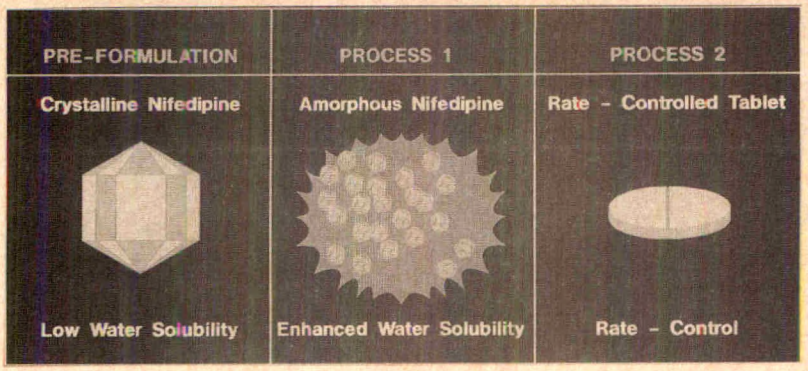


FIGURE 1. Overview of key process steps in insoluble drug absorption system (INDAS).

24-hour dosing form residence occurs. The implication of this limited solubility is an incomplete absorption and inability to deliver nifedipine to the circulation over the terminal phase of the dosing interval. A novel formulation technology, termed "insoluble drug absorption system" (INDAS), has been developed to deal with this problem using a 2-step process. Initially crystalline nifedipine is processed to produce an amorphous form of nifedipine, which has an inherently higher aqueous solubility. The amorphous nifedipine is then formulated into a rate-controlling tablet that provides for sustained release of the drug into the aqueous environment of the GI tract and resultant absorption by the intestinal mucosa over a 24-hour period (Figure 1). The design and physical characteristics of this rate-controlling matrix tablet have been optimized to achieve a release profile that is consistently maintained over a 24-hour period and that is also largely independent of external pH. The physical characteristics of the tablet during a simulated (in vitro) 24-hour dosage interval are summarized graphically in Figure 2. The gradual physical erosion and disintegration of the intact tablet to a finer dispersion of particles is designed to achieve a wide dispersal in the colon. This provides a longer and more consistent residence time within the large intestine, which results in prolonged, regular release and absorption of the amorphous nifedipine. Gradual, controlled tablet erosion is an important feature because it has been well established that the major differences in GI transit parameters between nondisintegrating and multiparticulate formulations arise in the large intestine, with nondisintegrating units showing a significantly more variable[5] and more rapid transit, which may preclude that particular dosage form from providing a consistently prolonged delivery and absorption profile.

The studies described in this report characterize the pharmacokinetic and transit characteristics of a sustained release formulation of nifedipine (Adalat SR, Miles Inc.) in healthy volunteers.

METHODS

Study 1: A multiple-dose comparative crossover, open label study in 24 young healthy male volunteers was conducted with both local ethical committee institutional review board and regulatory approval. All subjects gave written informed consent. Each subject received a 10-mg immediate-release nifedipine (N) capsule (Procardia) every 8 hours or 50 mg controlled-release nifedipine tablet (Adalat SR) once daily for 3 days. The regimens were administered in intervals separated by a week or longer. Blood samples (6 mL) for measurement

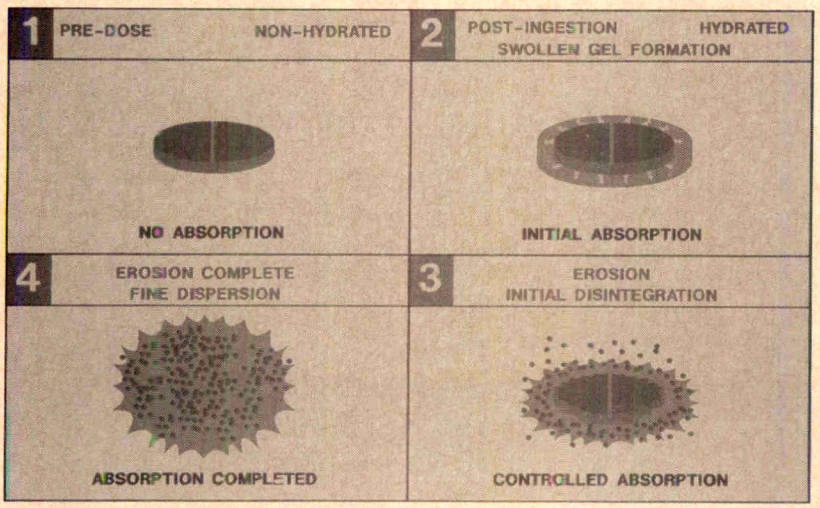


FIGURE 2. Overview of physical characteristics of nifedipine-SR during the release/absorption process.

of drug concentration were collected each morning predose to confirm attainment of steady-state conditions. Numerous blood samples were collected at frequent intervals (Table I) during day 3 to characterize the plasma level profile of the dosage regimens. Plasma nifedipine levels were analyzed using an in-house gas chromatographic method with electron capture detection with an accurate limit of detection set at 2 ng/mL.[6] The following standard noncompartmental pharmacokinetic parameters were determined for each regimen: area under the concentration-time curve (AUC); peak plasma levels (C_{max}); time of peak plasma nifedipine levels (T_{max}); trough plasma levels at 24 hours, peak-minimum fluctuations in plasma levels [$C_{max} - C_{min}/C_{min}$]; and apparent plasma nifedipine half-life ($t_{1/2}$). Data were compared using an analysis of variance model appropriate to the design of the study. A p value of <0.05 was considered significant.

Study 2: A single-dose open label study in 8 young healthy male volunteers was conducted with local ethics committee institutional review board approval. Following an overnight fast, all the volunteers received a single SR tablet (50 mg) labelled with samarium-153 (1 MBq). In vitro studies have demonstrated that neither the presence of the small quantity of samarium oxide nor the neutron activation procedure used to activate the stable samarium-152 to the gamma-emitting isotope samarium-153 influenced the release behavior of the formulation or the stability of the drug.[6] The tablet was administered with 100 mL of water containing 1 MBq of [^{99m}Tc]diethylenetriaminepentaacetic acid, which allowed an outline of the GI anatomy to be recorded. Subjects fasted for another 3 hours following ingestion of the tablet. Blood samples (16 mL) were collected predose (0), and 1, 2, 4, 6, 8, 10, 12, 16, 24, 30, 48, 60, and 72 hours postdose, and anterior scintigraphic images were taken at frequent intervals over the 24-hour postdose period. Plasma nifedipine concentrations were measured as detailed for study 1.

RESULTS

Study 1: Mean plasma nifedipine concentrations for both nifedipine formulations are shown in Table I and in Figure 3, and noncompartmental pharmacokinetic parameters are summarized in Table II. At the doses studied, SR was equivalent to N in divided doses in terms of extent of absorption: mean 387.1 versus 377.5, respectively, AUC_{0-24h}. Reflecting the controlled release characteristics of SR, the mean time to peak plasma concentration (T_{max}) was significantly longer for SR versus N, 3.9 hours versus 0.6 hours, respectively. The apparent half-life was also significantly longer following administration of SR (11.8 hours vs 3.0 hours), reflecting the prolonged absorption phase of the SR formulation. The magnitude of the peak plasma concentration was significantly lower, the trailing trough levels higher, and the

TABLE I Mean Steady-State Plasma Nifedipine Concentrations After Administration of Immediate- and Sustained-Release Dosage Forms (n = 24)

Time Post-dosing (h)	Plasma Nifedipine Levels (ng/mL)	
	Immediate-Release Formulation	Sustained-Release Formulation
0.00	4.41 ± 2.80	10.83 ± 5.64*
0.25	19.70 ± 42.64	
0.50	71.54 ± 48.63	
1.00	52.62 ± 24.19	22.38 ± 17.44*
1.50	34.87 ± 14.46	
2.00	26.11 ± 11.52	28.39 ± 23.16
4.00	11.40 ± 5.34	24.16 ± 16.75*
6.00	6.00 ± 3.06	16.55 ± 12.84*
8.00	3.52 ± 2.35	14.52 ± 10.38*
8.25	8.22 ± 5.19	
8.50	31.96 ± 25.77	
9.00	38.88 ± 16.05	
9.50	36.11 ± 11.50	
10.00	26.49 ± 12.24	15.83 ± 11.11*
12.00	11.00 ± 7.19	15.35 ± 10.23*
14.00	6.12 ± 2.87	
16.00	3.73 ± 2.93	14.75 ± 9.46*
16.25	3.55 ± 3.02	
16.50	13.72 ± 10.55	
17.00	26.85 ± 15.54	
17.50	26.44 ± 15.60	
18.00	24.54 ± 14.75	
20.00	12.18 ± 6.33	
22.00	7.39 ± 4.55	
24.00	4.54 ± 2.93	10.00 ± 7.52*
30.00		7.27 ± 5.73
36.00		3.96 ± 4.60
48.00		1.54 ± 2.76
60.00		0.51 ± 1.41
72.00		0.37 ± 1.02

*p ≤0.01 compared with immediate-release formulation.

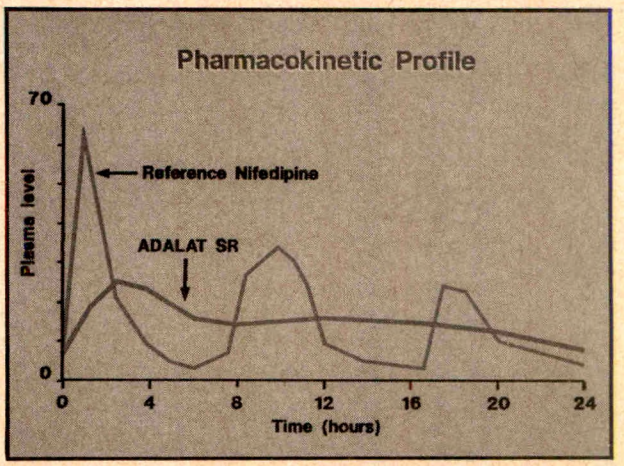


FIGURE 3. Mean plasma nifedipine concentrations in 24 subjects following administration on day 3 of conventional nifedipine capsules (N) (10 mg every 8 hours) and nifedipine-SR (Adalat SR) (50 mg once-daily).

TABLE II Summary Pharmacokinetic Parameters (n = 24)

	Reference Nifedipine Mean (SD)	Adalat SR Mean (SD)	p Value
AUC (0–24 hours)	377.5 (144.7)	387.1 (103.2)	NS
C_{av}	15.7 (6.0)	16.1 (10.4)	NS
C_{max}	84.4 (45.9)	31.3 (23.0)	<0.01
C_{24}	4.5 (2.9)	10.0 (7.5)	<0.01
T_{max}	0.6 (0.3)	3.9 (3.8)	<0.01
$T_{1/2}$	3.0 (1.4)	11.8 (6.8)	<0.01
$(C_{max} - C_{min}/C_{min}$	28.5 (14.5)	3.3 (2.8)	<0.01

AUC = area under the curve; C_{av} = average concentration; C_{max} = peak plasma concentration; C_{24} = trough 24-hour levels; T_{max} = time to peak plasma levels; $(C_{max} - C_{min})/C_{min}$ = peak minimum fluctuations in plasma levels; $t_{1/2}$ = plasma elimination half-life.

TABLE III Gastrointestinal Transit Characteristics

Subject Number	Transit Gastric Emptying (Min)	Small Intestine Transit (Min)	Colon Arrival (Min)	Nifedipine-SR Total Erosion* (Min)	Site of Disintegration
1	35	—	—	304	Small intestine
2	12	184	196	383	Proximal colon
3	57	128	185	619	Hepatic flexure
4	105	158	263	500	Proximal colon
5	59	138	197	354	Proximal colon
6	10	186	196	552	Hepatic flexure
7	33	329	362	440	Proximal colon
8	105	92	197	554	Sigmoid colon
Mean	52	173.6	228.0	463.3	
SEM	13.2	28.7	24.4	39.2	

SEM = standard error of the mean
*Time of first scintigraphic image at which disintegration of the matrix was observed.

magnitude of the peak-to-trough fluctuation also significantly lower with SR compared with N.

Study 2: Analysis of the scintigraphic images showed that in all subjects the dosage form was emptied intact from the stomach. GI transit parameters are summarized in Table III. Mean individual gastric emptying time was 52 minutes, with a range of 12–105 minutes. In most cases, the tablet reached the colon within 3–4 hours (i.e., 180–240 minutes) after dosing (mean, 228 minutes) (Figure 4). In all but one subject (number 1), the dosage form was still intact when it reached the colon, with disintegration occurring on average 7.7 hours or 463.3 minutes postadministration. In addition, shown in Figure 5 are the individual plasma nifedipine profiles for each subject over 24 hours with the appropriate segments of the GI tract indicated on the same time axis. The point of complete erosion of the tablet is also indicated in this figure.

DISCUSSION

These data demonstrate the pharmacokinetic characteristics of this novel sustained release formulation of nifedipine-SR administered once daily. The plasma nifedipine level profile following SR administration is characterized by a significantly prolonged absorption phase, consistent with the once-daily administration and low daily dose recommended for this product. Compared with conventional nifedipine capsules dosed every 8 hours, the SR formulation had a better plasma level profile, reduced peak-to-trough plasma level fluctuations, a later T_{max}, and an extended apparent $t_{1/2}$. Plasma levels remained relatively constant throughout the dosing interval without the peaks and valleys typical of conventional nifedipine.

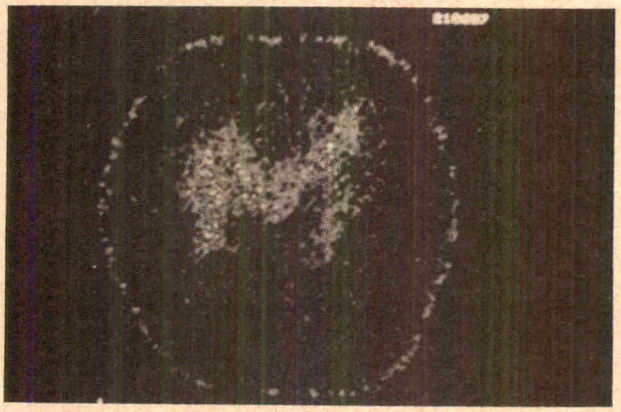


FIGURE 4. Scintigram of nifedipine-SR tablet disintegration in the gastrointestinal tract at 12.5 hours postdose. Location: proximal and transverse colon, showing spreading of tablet matrix residue.

The results of the scintigraphic imaging study have characterized the GI transit characteristics for this dosage form. The major site of residence and absorption was found to be the large intestine/colon. Absorption from the stomach is minimal. The GI transit parameters measured in this study confirm the now well-established range of values for gastric emptying, small intestine transit, and colonic residence. The mean gastric emptying time recorded for the once-daily dosage form (52 minutes) was consistent with the physiologic process known as the migrating myoelectric complex which generally causes emptying of the fasted stomach of any indigestible material over a 2-hour cycle.[7] Individual gastric emptying times were in the range of 10–105 minutes; this variability in emptying times in the fasted state is thought to depend on the time of arrival of the tablet in the stomach in relation to the contractual activity of the migrating myoeletric complex. The average small intestinal transit time (2.9 hours) was consistent with previous reports, which indicate that small intestinal transit is independent of dosage form design and feeding conditions and is typically about 3 hours.[8] The scintigraphic imaging study has also confirmed the physical characteristics of this matrix tablet, which results in a gradual erosion and disintegration and wide distribution in the colon during the absorption phase, thus achieving both controlled

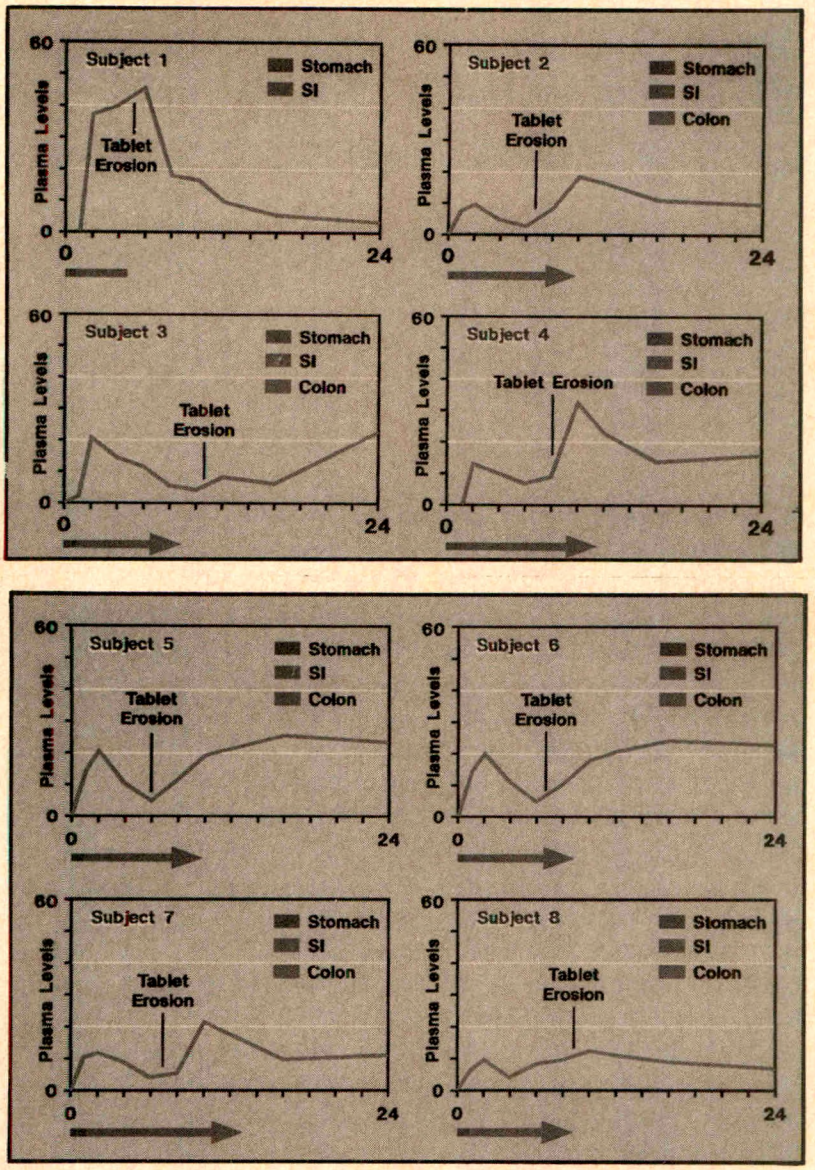


FIGURE 5. Individual plasma nifedipine concentration profiles following single administration of nifedipine-SR (50 mg). The corresponding gastrointestinal segment is indicated on the time axis. The time of erosion of the tablet is also noted.

release and controlled absorption of nifedipine throughout the 24-hour dosing interval.

Based on the established longer transit characteristics and greater dispersal properties of smaller multiple dosage units in the GI tract (particularly in the large intestine) compared with nondisintegrating units,[2] the pharmaceutical characteristics of this new medication-conserving dosage form of nifedipine should provide a relatively consistent and reliable absorption pattern over the 24-hour dosing interval and maintain control of blood pressure during the period. This is achieved with a low daily dose and a convenient regimen.

CONCLUSION

The new INDAS formulation of nifedipine conserves medication, yet provides for a prolonged absorption of nifedipine that ensures continuing plasma levels of nifedipine over the entire 24-hour dosing interval. Clinical confirmation of the therapeutic efficacy and safety characteristics of this novel dosage form should be based on evaluation of the diurnal pattern of blood pressure control over the full 24-hour dosage interval.

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Effectiveness of Once-Daily Monotherapy With a New Nifedipine Sustained Release Calcium Antagonist

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Data from 2 separate multicenter, double-blind clinical studies following the same protocol, except for the selection of doses, were pooled to evaluate the efficacy and tolerability of fixed doses of a new sustained-release (SR) formulation of nifedipine compared with placebo in 388 patients with mild to moderate uncomplicated essential hypertension. After a 3–6 week placebo washout period, the patients were randomized to receive either placebo or nifedipine SR-20 mg (study I only), 50 mg, 100 mg, or 150 mg (study II only). Among the 278 patients who completed 6 weeks of active therapy, mean supine diastolic blood pressure reductions from pretreatment baseline were 5.9, 9.3, 9.2, 11.1, and 13.2 mm Hg in the placebo, 20-, 50-, 100-, and 150-mg groups, respectively. The reductions achieved in each of the nifedipine SR groups were statistically significant versus baseline values ($p < 0.001$). All nifedipine-SR doses reduced supine systolic blood pressure significantly more than placebo ($p < 0.001$). In addition, there was a significant linear relationship between the log of the dose and the blood pressure reduction ($p < 0.05$). Automated ambulatory blood pressure recordings performed in 221 of the patients showed that the blood pressure was lowered evenly through the entire 24-hour dosing period. The doses that were effective and associated with the fewest adverse reactions were 20 mg and 50 mg once daily.

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Essential or primary hypertension is a common clinical diagnosis in the United States. Upward of 58 million people are believed to have high blood pressure, defined as blood pressure >140 mm Hg systolic or >90 mm Hg diastolic.[1] According to the Joint National Committee Report on high blood pressure, hypertension is the most common indication for the use of prescription medications in the United States.[1] Traditional stepped-care for the treatment of hypertension, ie, initial drug treatment with diuretics, has largely been replaced by individualization of therapy based on specific patient medical needs including concurrent disease states, potential drug interactions, impact on cardiovascular morbidity and mortality, and likelihood of adherence to a prescribed drug regimen (based on adverse effects, number of daily doses, and cost). A variety of drug classes are indicated for initial treatment of hypertension, namely, diuretics, β-adrenergic blockers, angiotensin-converting enzyme (ACE) inhibitors, and calcium antagonists.[1]

Calcium antagonists, also known as calcium ion influx inhibitors, are peripheral vasodilators that also reduce conduit artery wall stiffness.[2–4] Verapamil, diltiazem, and nifedipine are representatives, respectively, of the three subgroups diphenylalkylamine, benzothiazepine, and dihydropyridine, respectively, in the calcium antagonist class of antihypertensive drugs. These subgroups differ in their effects on myocardial contractility, cardiac conduction times of the sinoatrial and atrioventricular nodes, and resistance of arteriolar tone.[2–4] Although conventional formulations of verapamil, diltiazem, and nifedipine are effective for the treatment of hypertension, they have a short duration of action, requiring multiple daily dosing of immediate-release formulations. This may result in marked variability in gastrointestinal (GI) absorption, blood levels, and hemodynamic effects, which

may produce reflex tachycardia and release of renin and catecholamines.[2–6]

A new sustained-released (SR) formulation of nifedipine has been developed that provides reliable, controlled release through gradual absorption. The new preparation uses amorphous nifedipine in a complex hydrogel matrix system, based on an insoluble drug absorption system (INDAS; Elan Corp.). The matrix is designed to erode gradually and completely in a controlled and programmed process during its passage through the GI tract and to release readily absorbable noncrystalline nifedipine at distal sites within the GI tract in a predictable fashion over a full 24 hours. This formulation allows for once-daily dosing, which is generally associated with better compliance than more frequent dosing, particularly in the elderly.[7–10] Also of note is that this sustained-release tablet is completely dissolved in the GI tract and does not leave a "shell" remnant to be eliminated in the feces, as occurs with another delayed-release formulation that has been reported to cause gastric outlet obstruction.[11]

This article pools the results of 2 clinical trials conducted to evaluate the antihypertensive efficacy and tolerability of this new nifedipine SR formulation in 4 different doses, 20-, 50-, 100-, and 150-mg, administered once daily. The 2 different studies followed the same protocol, but one study dealt with 20-, 50-, and 100-mg nifedipine-SR and the other with 50-, 100-, and 150-mg. Thus, the doses common to both studies were placebo and the 50 mg and 100 mg doses.

METHODS

Four fixed doses of nifedipine-SR, administered once daily, were studied in adults with mild to moderate hypertension. The study design was placebo-controlled and used parallel treatment groups. Written informed consent was obtained from each patient, and the protocols were approved by each institutional review board. Outpatient men and non-pregnant, non-nursing women (practicing effective birth control or postmenopausal), ages 21–70 years, were eligible for enrollment. All patients were ambulatory, with mild to moderate essential hypertension, which was defined for this study as supine diastolic blood pressure (DBP) of 95–119 mm Hg, as determined by the average of the last 2 visits of the 3–6 week single-blind placebo baseline period. Patients were excluded from the study for any of the following reasons: severe hypertension (supine DBP > 119 mm Hg); history of accelerated hypertension; dissecting aortic aneurysm; cerebral or subarachnoid hemorrhage; asthma; congestive heart failure requiring drug therapy; cardiac arrhythmias; myocardial infarction within the previous 2 months; renal impairment (serum creatinine > 2 mg/dL or significant proteinuria); hepatic impairment; hypersensitivity to nifedipine or dihydropyridine analogues; or inability to provide written informed consent.

After the initial 3–6 week single-blind placebo washout period, eligible patients were randomly assigned to 1 of 5 parallel groups: placebo or 20-, 50-, or 100-mg nifedipine-SR (study I only) and placebo, 50 mg, 100 mg, or 150 mg nifedipine-SR (study II only). All patients received a single daily dose. The treatment schedule was continued unchanged for 6 weeks.

A history and physical examination, a 12-lead electrocardiogram, and collection of venous blood for laboratory tests were performed during the initial placebo-qualifying baseline period and within 7 days of the final study visit during active treatment. Laboratory tests included complete blood count, serum chemistry, urinalysis, and chest radiograph. Blood pressure measurements were obtained at each weekly visit or evaluation time. Supine, sitting, and standing manual blood pressure and heart rate were determined in duplicate (2–5 minutes apart), following the recommendations of the American Heart Association.[12] Patients were instructed to take their study medication in the morning without food except on evaluation days, when they were to report to the study center just prior to their next dose, i.e., 23–25 hours after the previous dose.

Adverse events were determined by questioning the patient at each weekly evaluation visit during the active treatment period. If the adverse events were intolerable and if deemed necessary, treatment was discontinued and the patient dropped from the study.

Patients were invited to participate in a 24-hour automated ambulatory blood pressure monitoring (ABPM). The blood pressures in these volunteers were measured every 15 minutes using a Pressurometer IV recorder (Del Mar Avionics, Irvine, California), which was gated to an electrocardiogram R wave. The ABPM was performed twice during the placebo-qualifying phase and twice during the double-blind treatment phase. The readings were averaged by hour for each subject. Blood pressure curves for the different treatment groups were computed using the individual averages. The data were smoothed using the 5-term Fourier series.[13–14]

To assess efficacy, reduction in trough supine

TABLE I Patient Demographics

Characteristic	Placebo	20 mg	50 mg	100 mg	150 mg
Number	98	50	98	98	44
Sex (% male)	49.0	30.0	49.0	41.8	50.0
Race (% white)	65.3	54	59.2	67.3	63.6
Mean age (years)	49.1	44.7	46.3	46.8	46.1
Mean weight (lb)	189.6	206.4	195.5	203.4	201.1

TABLE II Mean Blood Pressure Values Before and After 6 Weeks of Therapy with Nifedipine SR

	No. Patients	6-Week Post-Treatment Value	Δ(mm Hg)	p-Value
Supine DBP (mm Hg)				
Placebo	74	96.3	−5.9	NS
20 mg	40	94.2	−9.3	<0.001
50 mg	74	94.3	−9.2	<0.001
100 mg	65	92.8	−11.1	<0.001
150 mg	25	90.2	−13.2	<0.001
Supine SBP (mm Hg)				
Placebo	74	145.7	−5.0	NS
20 mg	40	144.6	−11.0	<0.001
50 mg	74	142.1	−10.8	<0.001
100 mg	65	140.9	−12.8	<0.001
150 mg	25	132.8	−13.5	<0.001

Δ = change from baseline at 6 weeks (study end point); DBP = diastolic blood pressure; SBP = systolic blood pressure.

DBP from baseline after 6 weeks of active therapy for each of the nifedipine treatment groups versus placebo was determined. A separate intent-to-treat analysis was performed on the data from patients who received the study drug and for whom blood pressure measurements were obtained but who did not complete 6 weeks of therapy. A secondary efficacy end point was 24-hour average blood pressure reduction, as determined by 24-hour ABPM. All comparisons of group means were made using a 1-sided Student's paired *t*-test. A p value ≤ 0.05 was considered to be statistically significant.

Log dose DBP response curves were constructed from group mean responses for the 20-, 50-, 100-, and 150-mg doses of nifedipine-SR using the placebo response during active treatment as the baseline. The best fit was determined by using linear regression analysis, correlation coefficient determination (r value), and the visual aid of French curves. A p value of ≤ 0.05 was considered to be statistically signficant.

The safety of the treatment was evaluated in all randomized patients on the basis of adverse events, which were rated as mild (discomfort without a significant effect in well-being), moderate (significant discomfort), or severe (severe or life-threatening discomfort).

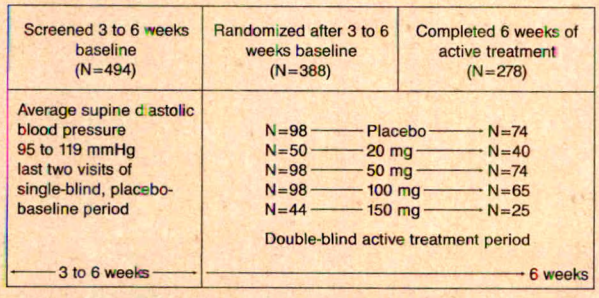


FIGURE 1. Patient enrollment and assignment to treatment groups.

RESULTS

Patients: Of the 388 patients randomized to the different treatment groups, 373 were included in the intent-to-treat analysis. The other 15 dropped out of the study prior to the first double-blind visit postrandomization. There were 278 patients who completed 6 weeks of therapy (74, 40, 74, 65, and 25 in the placebo, 20-, 50-, 100-, and 150-mg nifedipine treatment groups, respectively) and thus were evaluable for the primary efficacy analysis (Figure 1). All patients enrolled in the double-blind active treatment phase were included in the safety analysis. The treatment groups did not differ with respect to age, sex, race, or weight (Table I). Automated ABPM was performed in 221 patients; 69 in the placebo group and 19, 64, 47, and 22 in the nifedipine-SR 20-, 50-, 100-, and 150-mg groups, respectively.

Efficacy: Among the 278 patients who completed 6 weeks of therapy, the mean reductions from baseline in supine DBP were as follows: 5.9 mm Hg for placebo, 9.3 mm Hg for 20 mg, 9.2 mm Hg for 50 mg, 11.1 mm Hg for 100 mg, and 13.2 mm Hg for 150 mg (Table II). The reduction in supine DBP from baseline was statistically significant for all 4 active treatment groups ($p < 0.001$). In addition, for each active treatment group, the reductions in supine systolic blood pressure from baseline were significantly greater ($p < 0.001$) than that after placebo. Blood pressure responses in the intent-to-treat group were similar to those who completed 6 weeks of therapy (Table III). The reductions from baseline during active treatment with 20-, 50-, 100-, and 150-mg nifedipine were all significantly greater than placebo (supine DBP) among those who completed 6 weeks of therapy and those in the intent-to-treat groups.

The log-dose office DBP reductions from baseline are shown in Figure 2. There was a significant linear relationship between the log of the dose and the blood pressure reduction ($r = 0.87$, $p < 0.05$). The dose of nifedipine-SR that produced 50% of

the maximum DBP reduction was found to be 26 mg.

The log-dose 24 hour mean DBP of the automated ABPM is shown in Figure 3. The dose of nifedipine SR producing 50% of the maximum DBP reduction was 24 mg. There was a significant linear relation between dose and blood pressure responses ($r = 0.86$, $p < 0.05$).

The 24-hour automated ABPM patterns for active minus baseline periods for DBPs are shown in Figure 4. The patterns of blood pressure responses over the 24-hour period were similar except for the 20 mg dose, which produced little variation over the 24-hour period with approximately a 4.8 mm Hg reduction in DBP. These curves clearly illustrate that nifedipine SR in doses of 20-, 50-, 100-, and 150-mg was effective for 24 hours. The peak effect occurred approximately 5–6 hours after administration. The trough-to-peak ratios based on modeled mean data from the ABPM data were 0.91, 0.60, 0.65, and 0.74 for the 20-, 50-, 100-, and 150-mg treatment groups, respectively.

Safety: There were 290 patients randomized to receive nifedipine-SR 20–150 mg once daily and 98 to receive placebo during the active treatment period. Among those receiving nifedipine-SR, 148 (51%) experienced one or more adverse events compared with 36 (37%) in the placebo group. In the active treatment groups, the percentages of adverse reactions by dose were: 20 mg, 38%; 50 mg, 42%; 100 mg, 61%; and 150 mg, 64% (Table IV). The log dose–adverse event relation is shown in Figure 2. Edema, predominantly peripheral, and headache were the 2 most frequent complaints in the placebo group and all 4 nifedipine-SR treatment groups (Table IV). The overall incidence of adverse events was low in the 20- and 50-mg nifedipine groups and comparable with that of placebo. However, the incidence of adverse events

TABLE III Mean Blood Pressure Values Before and After Treatment with Nifedipine SR (Intent-to-Treat Analysis)

	No. Patients	Post-Treatment Value	Δ (mm Hg)	p value
Supine DBP (mm Hg)				
Placebo	97	97.7	−5.5	NS
20 mg	47	95.1	−8.5	<0.001
50 mg	96	95.2	−8.2	<0.001
100 mg	94	94.4	−9.4	<0.001
150 mg	39	93.3	−10.4	<0.001
Supine SBP (mm Hg)				
Placebo	97	149.1	−4.2	NS
20 mg	47	146.1	−9.8	<0.001
50 mg	96	144.7	−8.4	<0.001
100 mg	94	142.7	−11.5	<0.001
150 mg	39	145.7	−9.3	<0.001

Δ = change from baseline at last valid double-blind visit; DBP = diastolic blood pressure; SBP = systolic blood pressure; NS = difference not significant.

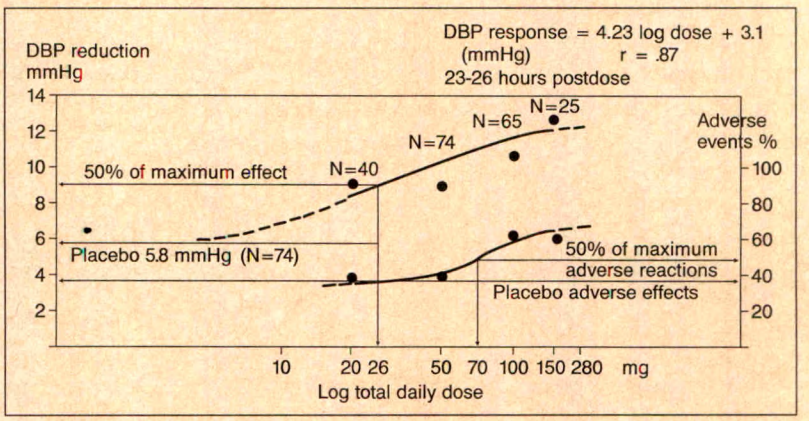


FIGURE 2. Office supine diastolic blood pressure (DBP) in 278 patients who completed 6 weeks of treatment with placebo (n = 74) or sustained-release nifedipine 20 mg (n = 40), 50 mg (n = 74), 100 mg (n = 65), or 150 mg (n = 25).

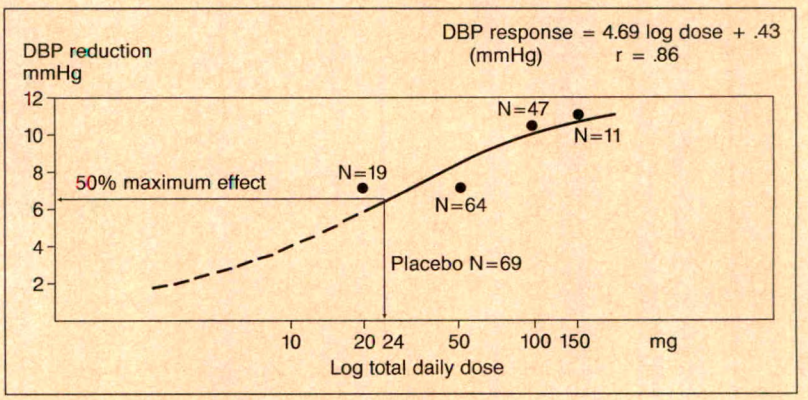


FIGURE 3. The 24-hour average automated ambulatory diastolic blood pressure (DBP) monitoring in 210 patients after placebo (n = 69) or sustained-release nifedipine 20 mg (n = 19), 50 mg (n = 64), 100 mg (n = 47), or 150 mg (n = 11).

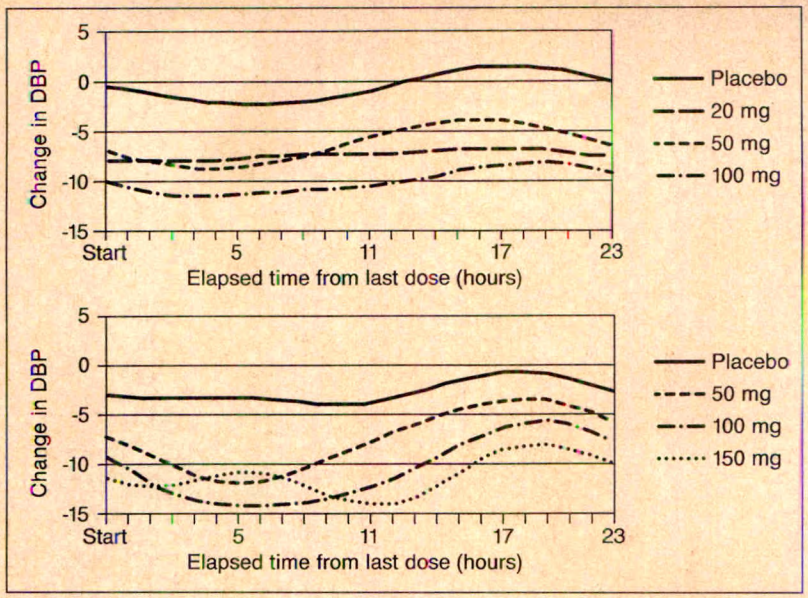


FIGURE 4. 24-hour mean of automated ambulatory blood pressure monitorings after placebo or sustained-release nifedipine 20 mg, 50 mg, 100 mg, or 150 mg. DBP = diastolic blood pressure

increased markedly with doses above 50 mg once daily.

DISCUSSION

Nifedipine-SR, a new sustained-release matrix formulation of amorphous nifedipine, was documented by manual and ambulatory blood pressure determinations to reduce blood pressure significantly at trough and throughout the daily dosing period in doses of 20-, 50-, 100-, and 150-mg administered once daily. The 20-mg dose, the lowest dose included in the study, had a clinically meaningful effect, making it the lowest effective dose of any once-daily nifedipine formulation. The blood pressure reductions were shown to exhibit a log dose-blood pressure reduction relation. The doses that were both effective and associated with the fewest adverse reactions were 20 mg and 50 mg once daily. The automated ABPM findings demonstrated that the decrease in blood pressure at peak effect was not excessive (trough to peak ratio >0.6) and that the blood pressure reductions persisted throughout the 24-hour dosing interval. This may be advantageous for the use of nifedipine in the treatment of hypertension and certainly offers clinicians another therapeutic choice for their patients.

TABLE IV Adverse Experiences Reported in 3% or More of Patients Treated with Placebo or Nifedipine-SR

Adverse Reaction	Placebo (n = 98) %	20 mg (n = 50) %	50 mg (n = 98) %	100 mg (n = 98) %	150 mg (n = 44) %
Overall	37	38	42	61	64
Edema	3	4	9	24	23
Dizziness	7	4	8	12	23
Headache	21	18	21	31	30
Constipation	1	4	3	5	9
Vasodilation	3	4	8	7	0
Tachycardia	3	2	2	6	5
Asthenia	2	0	3	6	14
Nausea	1	4	1	5	5
Dyspepsia	2	0	4	2	9

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Hypertension In The Elderly With a Special Focus on Treatment With Angiotensin-Converting Enzyme Inhibitors and Calcium Antagonists

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Age-related changes (e.g., decrease in plasma renin activity and total body potassium, increase in plasma catecholamines, volume depletion) need to be taken into account when selecting an antihypertensive agent for the elderly patient. A number of large scale clinical trials (e.g., Systolic Hypertension in the Elderly Program, Veterans Administration Cooperative Study, European Working Party on High Blood Pressure in the Elderly) have demonstrated that antihypertensive therapy with diuretics substantially reduces cardiovascular mortality and stroke incidence. However, since diuretics, even potassium-sparing agents, may induce hypokalemia, newer antihypertensive agents (angiotensin-converting enzyme [ACE] inhibitors and calcium antagonists) may also be appropriate as first-line monotherapy for this patient population. ACE inhibitors are effective antihypertensive agents and are associated with a lower rate of adverse effects than diuretics, β blockers, and centrally acting agents. Nevertheless, periodic monitoring of serum potassium, creatinine levels, and renal function is advisable. An important feature of calcium antagonists is that they lower blood pressure with no negative effect on serum lipids or glucose metabolism. Typically, they have few side effects, peripheral edema being the most commonly reported. A recent double-blind randomized study comparing a new sustained release nifedipine formulation and the ACE inhibitor lisinopril found the 2 drugs equivalent in efficacy with no differences in the rate of adverse events.

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Elderly is an adjective meaning between middle and older (elder) ages. Many terms have been used to categorize persons of increasing chronologic age. Hall's classification (Table I) is one that appeases most adults as they mature.[1] The need to differentiate the elderly from the general population is especially critical when selecting and prescribing antihypertensive agents, as the effect of age often reduces the usual adult daily dose. Moreover, a simplified, low-dosage regimen may be the key to therapeutic success when prescribing for this highly medicated and often noncompliant age group.

MAKING THE DIAGNOSIS OF ESSENTIAL HYPERTENSION IN THE ELDERLY

The diagnosis of diastolic hypertension requires confirmation of an average seated diastolic blood pressure ≥ 90 mm Hg on 3 consecutive visits, generally made over several weeks or more (Table II).[2] The diagnosis of isolated systolic hypertension requires confirmation of an average seated systolic blood pressure ≥ 160 mm Hg when the diastolic blood pressure remains < 90 mm Hg on 3 consecutive visits (Table II).[2]

When diastolic blood pressure at the initial visit is between 90 and 104 mm Hg, or when the initial systolic blood pressure level is between 160 and 200 mm Hg, repeated measurements on subsequent visits will fall into the normal range without drug therapy in approximately 50% of patients. Hence, the diagnosis needs to be confirmed prior to making a commitment to long-term therapy.

Pseudohypertension is when the brachial artery is so hardened and stiff that it cannot be compressed normally by the air pressure in the bladder of the blood pressure cuff, causing artefactual elevations in the level of systolic blood pressure. It is suspected clinically by the presence of a positive Osler's sign, in which the radial artery fails to collapse and remains easily palpable even after blood flow is occluded by raising the cuff pressure above the systolic pressure.[3] Pseudohypertension

TABLE I Hall's Classification of Aging

Term	Age Range (years)
Mature Adult	55–67
Aging	68–76
Elderly	77–86
Aged	87–99
Born lucky	≥100

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TABLE II Classification of Blood Pressure in Adults

Blood Pressure Range (mm Hg)	Category
Diastolic	
<85	Normal
85–89	High normal
90–104	Mild hypertension
105–114	Moderate hypertension
≥115	Severe hypertension
Systolic*	
<140	Normal
140–159	Borderline isolated systolic hypertension
≥160	Isolated systolic hypertension

*When diastolic blood pressure is <90 mm Hg.
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can be confirmed by a direct measurement of intraarterial pressure that is markedly lower than the recorded cuff pressure.

Pseudohypotension occurs in a few elderly patients who have a difference in systolic blood pressure ≥20 mm Hg between the left and right arms. The condition is due to atherosclerotic stenosis of the subclavian artery, suspected by detection of an infraclavicular bruit on the side of the arm with the lower blood pressure. In this setting, diagnosis and management decisions must be based on blood pressure readings in the arm with the higher value.

Renovascular hypertension is suspected in elderly patients when diastolic hypertension is abrupt in onset, or when blood pressure that was previously easy to control becomes more resistant to therapy.[4] Vetrovec and colleagues[5] performed abdominal angiography in 116 hypertensive patients (average age 57 years) undergoing diagnostic coronary angiography. Renal artery stenosis (>50% narrowing of one or both renal arteries) was present in 27 of the 116 patients (23%). The prevalence of atherosclerotic renal artery stenosis is also increased 2-fold in patients with diabetes mellitus,[6,7] especially those with proteinuria.

HEMODYNAMIC FEATURES OF HYPERTENSION IN THE ELDERLY

The Baltimore Longitudinal Study on Aging[8] showed no decrease in resting or exercise cardiac output with advancing age in healthy, active subjects free of cardiovascular disease. However, in relatively healthy hypertensive subjects, most studies have shown a lower cardiac output and a higher total peripheral resistance in elderly compared with younger individuals.[9,10] Antihypertensive therapy should be selected to reduce the elevated total peripheral resistance because it is the hemodynamic abnormality responsible for the hypertension.

The increase in total peripheral resistance in elderly hypertensive patients is accompanied by regional increases in peripheral resistance in certain target organs. For example, renal vascular resistance increases progressively with advancing age in hypertensive patients.[11] Messerli and coworkers[9] reported average renal blood flows of 674 versus 1,110 mL/min and average renal vascular resistances of 1,691 versus 1,012 units, respectively, in elderly compared with young patients with similar degrees of essential hypertension.

HUMORAL FEATURES OF HYPERTENSION IN THE ELDERLY

With increasing age, the renin-angiotensin system is suppressed in both normotensive and hypertensive individuals, as evidenced by the 4 studies listed in Table III. Weidmann et al[12] found that average plasma renin activity was approximately 50% lower in elderly compared with younger healthy individuals. Zozaya et al[13] noted a 62% lower average plasma renin activity in a much larger sample of subjects. Noth et al[14] confirmed the lower plasma renin activity values of normotensive and hypertensive elderly subjects and found a low renin profile in 9 of 15 (60%) elderly hypertensives, a prevalence of low renin hypertension similar to the 45% reported subsequently by Gavras et al[15] in elderly patients. Ruddy and associates[16] reported lower plasma renin activity values in hypertensive versus normotensive elderly subjects and found an inverse correlation between plasma renin activity and age ($r = -0.26$, $p = 0.009$). Bielen et al[17] noted that plasma renin activity reached its nadir by age 60 years, with little or no further decrease between the ages of 60 and 83 years. The lower plasma renin activity of elderly individuals is most likely related to lower activity of renin enzyme[12] rather than lower levels of angiotensinogen substrate.[14] Although some investigators have found slightly lower aldosterone values associated with the low renin profile of elderly subjects,[12,13] a few have not.[14]

A low plasma renin activity would blunt the antihypertensive efficacy of therapy with angioten-

TABLE III Ambulatory Plasma Renin Activity in Elderly Versus Young Individuals with Normal or High Blood Pressure

Reference	BP	Age (years)	No.	PRA (ng/mL/h)	Comments
Weidmann et al[12]	N	Elderly (62–70)	7	0.96*	Dietary sodium 120 mEq/day in both groups
	N	Young (20–30)	24	1.99	
Zozaya et al[13]	N	Elderly (75)	40	1.60*	24-hour sodium excretion averaged 116 and 137 mEq in the elderly and young groups, respectively
	N	Young (39)	37	4.17	
Noth et al[14]	N	Elderly (50–58)	19	2.65*	Low sodium (10 mEq/day) diet
	N	Young (20–29)	17	9.10	
	H	Elderly (47–61)	15	1.72*	9 of 15 (60%) low renin
	H	Young (18–30)	11	3.70	2 of 11 (18%) low renin
Ruddy et al[16]	N	Elderly (69)	39	2.9†	Unrestricted diet
	H	Elderly (71)	81	1.2	

*$p < 0.05$, comparison of PRA between elderly and young subjects.
†$p < 0.05$, comparison of PRA between hypertensive and normotensive elderly subjects.
BP = blood presssure; H = high; N = normal; PRA = plasma renin activity.

sin-converting enzyme (ACE) inhibitors if the mechanism of action of ACE inhibitors was limited solely to reduction in angiotensin II levels and if the specific actions on tissue ACE activity in the kidney, heart, brain, arterial wall, etc. were reflected accurately by the plasma levels of ACE and plasma renin activity. However, the action of most ACE inhibitors includes stimulation of vasodilator prostaglandins[18,19] and kinins such as bradykinin.[18,20] Moreover, renin and angiotensin are synthesized locally in many tissues where the local concentrations of angiotensin might exceed the plasma level and modulate vascular resistance and cellular hypertrophy.[21,22] Indirect evidence that ACE inhibitors have important activity on the tissue renin–angiotensin or other humoral systems includes the observation that ramipril reduced blood pressure in nephrectomized patients whose baseline plasma renin level was hardly detectable.[23]

Plasma catecholamines increase with age in both hypertensive and normotensive individuals.[9,24,25] There is, however, a reduced responsiveness to certain adrenergic stimuli[26] and diminished sensitivity of the baroreceptor reflex.[27] The blood pressure-lowering effect of central α agonists[28] and peripheral α blockers[29] would be increased in the setting of higher plasma catecholamines.

Atrial natriuretic peptide levels increase with age,[30] perhaps as a compensatory response to declining cardiac function. Low-dose infusions of atrial natriuretic peptide suppress plasma renin activity[31] and reduce vasoconstriction.[32,33] A decrease in the number of renal binding sites for atrial natriuretic peptide would help explain the impaired natriuresis typical of the aging kidney[34] but has not been documented.[30] Accentuation of the action of atrial natriuretic peptide by inhibition of its enzymatic breakdown could reduce blood pressure by a combined diuretic and vasodilator effect.[35,36]

BODY COMPOSITION IN THE ELDERLY

The classic Evan's blue dye studies of 90 patients (only 7 of whom were age ≥55 years) by Gibson and Evans in 1937[37] demonstrated that the blood volume compartments decrease with advancing age. Fulop and associates[38] used more modern isotopic techniques to measure total body water, lean body mass, exchangeable sodium, and the volumes of the plasma and extracellular, intracellular, and interstitial spaces in 40 healthy elderly and 20 young white individuals. Their results are summarized in Table IV. A lower total body water and lean body mass were found in healthy elderly women but not men. Total extracellular fluid volume did not differ in elderly versus young subjects but plasma volume was higher, especially in women. Weidmann and coworkers[12] reported no differences in either total blood volume (25.1 vs 24.4 mL/cm height) or plasma volume (15.3 vs 14.4 mL/cm height) in 8 normotensive elderly men and women (age 62–70 years) compared with 8 younger

TABLE IV Volume Compartment Characteristics in Healthy Elderly and Young Men and Women

	Men		Women	
	Elderly	Young	Elderly	Young
Total body water (mL/kg)	580 ± 54*	586 ± 64	442 ± 57	531 ± 90
Intracellular volume (mL/kg)	376 ± 42	378 ± 42	248 ± 26	329 ± 65
Extracellular volume (mL/kg)	204 ± 37	208 ± 31	193 ± 19	192 ± 31
Interstitial volume (mL/kg)	157 ± 20	168 ± 21	149 ± 21	173 ± 42
Plasma volume (mL/kg)	47 ± 6	43 ± 8	45 ± 10	30 ± 5
Exchangeable sodium (mEq/kg)	38 ± 7	41 ± 6	37 ± 4	39 ± 7
Lean body mass (g/kg)	790 ± 78	801 ± 88	604 ± 78	725 ± 113

*Standard deviation.
Reprinted with permission from Gerontology.[38]

TABLE V Antihypertensive Therapy in SHEP: Blood Pressure Lowering Effect of Diuretic With or Without Atenolol

	Placebo	Active Treatment
No.	2,371	2,365
Baseline	170/76	171/77
5 years	155/71	144/68
Change	−15/−5	−27/−9

SHEP = Systolic Hypertension in the Elderly Program.
Reprinted with permission from JAMA.[55]

TABLE VI Antihypertensive Therapy in 672 Elderly Men: Diuretic Monotherapy

	HCTZ	
	25–50 mg/day	50–100 mg/day
No.	342	330
Baseline	158/99	157/98
10 weeks	140/89	136/89
Change in blood pressure	−18/−10	−20/−10
K^+ < 3.5 mEq/liter	19%	32%

HCTZ = hydrochlorothiazide.
Reprinted with permission from Hypertension.[56]

men and women (age 20–30 years). However, Messerli et al[9] compared younger and older hypertensive men and women. Total blood volume was lower in the older hypertensives (4.10 vs 4.64 liters, $p < 0.03$) and correlated inversely with the total peripheral resistance. Volume depletion in elderly hypertensive patients with injudicious use of diuretics could lead to increased susceptibility to dehydration and orthostatic hypotension.

Total body potassium is decreased significantly in the elderly.[39,40] Fulop and coworkers[38] reported values of 44.9 vs 51.3 mmol/kg in elderly compared with younger men, and 34.1 vs 44.2 mmol/kg in elderly compared with younger women. A large proportion of the lower total body potassium in the elderly is related to the reduction in lean body mass. Black individuals often have lower dietary intakes of potassium,[41] but total body potassium tends to be higher than in gender- and age-matched control whites, largely because of greater lean body mass.[42] The decreased total body potassium content of elderly patients emphasizes the importance of careful monitoring of the serum potassium level during diuretic therapy, especially if dietary potassium intake is limited.

Intracellular calcium levels tend to be increased in patients with essential hypertension and to contribute to the vasoconstriction and increase in total peripheral resistance.[43,44] Resnick and colleagues [45,46] have developed the hypothesis that there is an altered ("mirror image") distribution of calcium and magnesium between the intracellular and extracellular compartments in essential hypertension, especially in low renin patients who exhibit lower serum levels of ionized calcium. Zozaya et al[13] also found a lower serum level of ionized calcium in elderly patients, with a positive correlation between the level of ionized calcium and plasma renin activity. A lower level of extracellular calcium and a higher level of intracellular calcium would enhance the blood pressure lowering effects of calcium antagonists.[47]

TREATMENT OF HYPERTENSION IN THE ELDERLY

General: Several excellent reviews address the treatment of diastolic hypertension in elderly individuals.[48–54] In addition, recently published data from the Systolic Hypertension in the Elderly Program (SHEP) provide guidelines for the treatment of isolated systolic hypertension in the elderly.[55]

Active treatment in the SHEP trial began with a very low dose (12.5 mg daily) of the diuretic chlorthalidone, which was increased to 25 mg daily if systolic blood pressure remained >160 mm Hg or had been reduced from baseline by <20 mm Hg. A low dose of atenolol (initially 25 mg, then 50 mg daily) was subsequently added as necessary to achieve goal systolic blood pressure. The 5-year changes in blood pressure in the active treatment and placebo groups are summarized in Table V. Serum potassium levels were monitored closely, and supplemental potassium was prescribed for all patients who developed a level of 3.2 mEq/liter or lower, which occurred in 3.9% of participants. The SHEP trial demonstrated the efficacy of lowering systolic blood pressure for the prevention of stroke, but was not a comparative study of a thiazide diuretic and atenolol.

A recently published Veterans Administration Cooperative Study compared the use of low dose (25–50 mg daily) and high dose (50–100 mg daily) hydrochlorothiazide (HCTZ) for 10 weeks in 690 elderly men (mean age 64 years) with diastolic hypertension.[56] The results are summarized in Table VI and demonstrate that low dose HCTZ produced >90% as much blood pressure reduction as did the higher dose. Hypokalemia, defined as a serum potassium level <3.5 mEq/liter, occurred in 32.3% of the high-dose HCTZ group and 18.6% of the low dose HCTZ group. The incidence of hypokalemia in this study is comparable with a 27.5% (50 mg HCTZ daily) and 50% (100 mg HCTZ daily) frequency of hypokalemia reported in an earlier Veterans Administration cooperative

study conducted with nonelderly men (average age 50 years).[57] These data suggest that, despite the lower total body potassium content of elderly individuals, diuretic-induced hypokalemia occurs with a similarly high prevalence in both elderly and nonelderly hypertensive patients.

Elderly hypertensive patients demonstrate a reduction in blood pressure that is even greater than that of younger patients who receive diuretic monotherapy.[58] Diuretic-based therapy (25–50 mg HCTZ plus 50–100 mg triamterene versus placebo) was also used in the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial of 840 elderly patients (mean age 72 years) with diastolic hypertension.[59] The average follow-up period was 4.6 years. Use of a potassium-sparing diuretic led to only modest differences in the serum potassium level in the actively treated group (4.05 mEq/liter) compared with the placebo-treated group (4.25 mEq/liter).[60]

The results from diuretic-based trials of antihypertensive therapy (versus placebo) in the elderly suggest a clear benefit in the risk of cardiovascular complications. In SHEP, the total stroke incidence was reduced by 36% ($p < 0.003$); nonfatal and fatal coronary heart disease events were reduced 25%. In EWPHE, total cardiovascular mortality was reduced 27% ($p = 0.037$) due largely to a 38% reduction in coronary heart disease mortality ($p = 0.036$); stroke mortality was reduced by 32%. Both the SHEP and EWPHE trials used special measures to reduce the risks of hypokalemia. As demonstrated by the Veterans Administration trial, however, hypokalemia can occur in as many as 18.6% of unsupplemented elderly hypertensive patients even when the dose of HCTZ is reduced to 25–50 mg daily.[56] A decline in renal function, defined as a 50% increase in serum creatinine after the first year, occurred in 44% of patients following institution of diuretic-based therapy in the EWPHE trial;[61] results from the SHEP trial are not yet analyzed.

ACE INHIBITORS

Table VII provides a list of the ACE inhibitors now marketed in the United States. The preceding discussion of lower plasma renin activity levels in the elderly would suggest that ACE inhibitors might be less efficacious in elderly compared with younger individuals. The data, however, demonstrate efficacy in elderly hypertensives, with little or no difference in the magnitude of the reduction in blood pressure when younger and older patients are compared.

TABLE VII Angiotensin-Converting Enzyme Inhibitors Marketed in the United States*

Generic Name	Trade Name(s)
Benazapril	Lotensin
Captopril	Capoten
Enalapril	Vasotec
Fosinopril	Monopril
Lisinopril	Prinivil, Zestril
Quinapril	Accupril
Ramipril	Altace

*As of April 1992.

A large multicenter trial on 975 hypertensive patients age ≥65 years treated with captopril was reported by Jenkins et al.[62] The results demonstrated effective reduction of blood pressure without serious hypotensive episodes or adverse effects on renal function. In smaller trials, efficacy of ACE inhibitors in elderly hypertensives has been shown for benazepril,[63] captopril,[64–66] enalapril,[67,68] lisinopril,[69,70] quinapril,[71,72] ramipril,[73] and others.[74,75]

Bonus effects of ACE inhibitors for the treatment of hypertension in the elderly include their beneficial effects on congestive heart failure,[76,77] regression of left ventricular hypertrophy,[78,79] and slowing of the rate of progression of renal failure,[80] especially in diabetic patients.[81]

As a class, the ACE inhibitors have no deleterious effects on serum lipids[82] and may even blunt the adverse lipid changes and magnitude of potassium loss associated with short-term thiazide diuretic therapy.[83] Glucose metabolism and insulin levels are unaltered by ACE inhibitor therapy.[84,85] Unlike the β blockers, there is no evidence that ACE inhibitors are cardioprotective following acute myocardial infarction,[86] but they may reduce the left ventricular dilation and increased filling pressure after anterior myocardial infarction, leading to improved exercise tolerance.[87]

The ACE inhibitors have a lower rate of adverse effects than do the diuretics, β blockers, or centrally acting agents. In particular, they do not impair exercise tolerance, decrease cardiac contractility or conduction (or coronary blood flow), reduce renal or cerebral blood flow, alter mental acuity, or induce sexual dysfunction. A bothersome and relatively prevalent adverse effect, however, is a dry cough.[88] This effect is especially germane in elderly patients because of their increased propensity to cough as related to comorbid illnesses, such as chronic obstructive pulmonary disease, acute respiratory infections, and congestive heart failure. For unexplained reasons, the cough occurs more commonly in women than in men,[88–90] and it thus

TABLE VIII Calcium Antagonists Marketed in the United States*

Generic Name	Trade Names
Bepridil	Vascor
Diltiazem	Cardizem, Cardizem SR, Cardizem CD
Felodipine	Plendil
Isradipine	DynaCirc
Nicardipine	Cardene
Nifedipine	Adalat, Procardia, Procardia XL
Nimodipine	Nimotop
Verapamil	Calan, Calan SR, Isoptin, Isoptin-SR, Verelan

*As of April 1992.

becomes even more prevalent in the elderly, the majority of whom are women. The cough is specific to ACE inhibitors as a class and, if truly drug-related, does not improve by converting from one ACE inhibitor to another.

Other adverse effects of ACE inhibitors include rash, hyperkalemia, acute worsening of renal function in the presence of bilateral renal artery stenosis, and rarely, angioneurotic edema. The rash occurs in 2–5% of patients, is usually macular, and responds to discontinuation of the drug. Hyperkalemia is an infrequent adverse effect of ACE inhibitors in patients with uncomplicated hypertension but occurs more often in patients with mild-to-moderate renal failure, especially if there is concomitant use of nonsteroidal antiinflammatory drugs.[91] The mechanism is related to the ACE inhibitor-induced decrease in aldosterone production associated with the reduced levels of angiotensin II. The decrease in glomerular filtration rate with advancing age, the frequent use of nonsteroidal antiinflammatory agents, and the increased prevalence of hypoaldosteronism in the elderly[92] all suggest careful attention to the use of potassium supplements, as well as intermittent monitoring of serum potassium and creatinine levels following prescribing of ACE inhibitors to elderly patients. Acute renal failure is an uncommon but feared complication of ACE inhibitor therapy in patients with bilateral renal artery stenosis[93] and other high renin states for which maintenance of glomerular filtration rate is dependent on high resistance in the renal efferent arteriole.[94]

CALCIUM ANTAGONISTS

Table VIII provides a list of the calcium antagonists now marketed in the United States. Amlodipine, felodipine, isradipine, nicardipine, and nifedipine are dihydropyridine derivatives. Calcium antagonists, such as diltiazem,[95,96] felodipine,[97] isradipine,[98] nicardipine,[99] nifedipine,[100,101] verapamil,[102] and others[103] have proven effective blood pressure-lowering agents in elderly hypertensives.

Buhler and associates[104–106] first reported that the reduction in blood pressure with calcium antagonists correlated directly with the height of the blood pressure and the age of the patient and inversely with the plasma renin activity. This led to the view that calcium antagonists were especially effective in older and low renin patients. Subsequent studies, however, have demonstrated equal efficacy in both older and younger hypertensives,[51,107,108] as well as black and white hypertensives.[108,109]

Bonus effects of calcium antagonists for the treatment of hypertension in the elderly include their beneficial effects on angina pectoris,[110] possible regression of left ventricular hypertrophy,[78,111,112] preservation or improvement in glomerular filtration rate and renal blood flow,[113–115] and decrease in proteinuria in some diabetics.[116] Calcium antagonists exert no deleterious effects on serum lipids or glucose metabolism,[82,117] and are under active investigation with regard to prevention of the progression of atherosclerosis.[118,119]

Adverse effects are relatively infrequent but include peripheral edema, dizziness, flushing, and constipation and may be dose related.[120] Severe rashes may occur more frequently than anticipated originally.[121] Mild cardiodepressant effects of verapamil and diltiazem (but not the dihydropyridines, e.g., nifedipine) limit their use in patients with advanced left ventricular systolic dysfunction, sick sinus syndrome, or atrioventricular node disease, especially if used in combination with β blockers.

When calcium antagonists are used in the management of patients with severe hypertension, a useful adage is "the higher the pressure, the greater the fall." Too rapid of a reduction in blood pressure can be associated with ischemic T-wave changes in patients with coronary artery disease[122] as well as in otherwise uncomplicated hypertensive patients with echocardiographic left ventricular hypertrophy.[123]

DOUBLE-BLIND, RANDOMIZED, COMPARATIVE TRIALS OF MONOTHERAPY FOR HYPERTENSION IN THE ELDERLY

There are very few large, double-blind, randomized studies that provide a comparison of monotherapy with different classes of antihypertensive drugs in elderly patients. The largest is a recently published trial comparing 16 weeks of therapy with a β blocker (atenolol, 50–100 mg daily), an ACE inhibitor (enalapril, 5–20 mg once daily) and a calcium

TABLE IX Comparison of Calcium Antagonist, β Blocker, and Angiotensin-Converting Enzyme Inhibitor Monotherapy in Elderly Hypertensive Women

	Diltiazem	Atenolol	Enalapril
No.	79	79	84
Baseline BP (mm Hg)	161/98	165/99	166/98
Week 16 BP (mm Hg)	147/84	154/88	153/88
Change in BP (mm Hg)	−14/−14	−11/−11	−13/−11
Adverse events reported (%)	54	53	46

*Reduction in diastolic blood pressure ≥ 10 mm Hg to < 90 mm Hg.
BP = blood pressure.
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TABLE X Comparison of Calcium Antagonist and Angiotensin Converting-Enzyme Inhibitor Monotherapy in Elderly Hypertensive Men and Women*

	Nifedipine-SR	Lisinopril
No. of patients	35	36
Baseline supine BP (mm Hg)	168/100	165/100
Week 10 supine BP (mm Hg)	155/91	154/91
Change in supine BP (mm Hg)	−13/−10	−11/−8
Goal BP (%)	46	50
Adverse events reported (%)	46	44

*Data on file, Pharmaceutical Division, Miles Inc.
†Reduction in diastolic blood pressure ≥ 10 mm Hg or to ≤ 90 mm Hg.
BP = blood pressure.

channel blocker (sustained release diltiazem, 60–180 mg twice daily) in 242 women age ≥ 65 years with a diastolic blood pressure between 95–114 mm Hg.[124] The results are summarized in Table IX and indicate that all three classes of drugs were effective in lowering diastolic blood pressure with no significant differences in the rate of adverse events. Although there was a trend toward worse scores on quality-of-life measures for the atenolol group, the findings were variable over time and reached statistical significance on only 1 occasion.

Another smaller, but randomized, double-blind trial has recently been completed comparing monotherapy with two classes of antihypertensive drugs in elderly men and women.[125] Patients aged ≥ 64 years with a diastolic blood pressure of 95–114 mm Hg were randomized to receive either a new sustained release formulation of nifedipine (Adalat-SR 10–100 mg once daily; Miles) or lisinopril (Prinivil 5–40 mg once daily; Merck Sharp and Dohme) for 10 weeks following a 4-week placebo run-in period. Table X provides a summary of the results and Figure 1 demonstrates the pattern of diastolic blood pressure decrease as recorded by 24-hour ambulatory monitoring after 8 weeks of treatment. There was equivalent efficacy of sustained-release nifedipine and lisinopril, with no differences in the rate of adverse events.

CONCLUSIONS

Only 2 clinical trials, SHEP and EWPHE, have thus far documented long-term decreases in cardiovascular morbidity and mortality in elderly hypertensive patients receiving antihypertensive therapy, and both used diuretic-based therapy. Data from short-term trials in elderly hypertensives suggest that ACE inhibitors, β blockers, and calcium antagonists are similary effective in lowering elevated blood pressure. Selection of a particular drug for first-line therapy will often be based on the

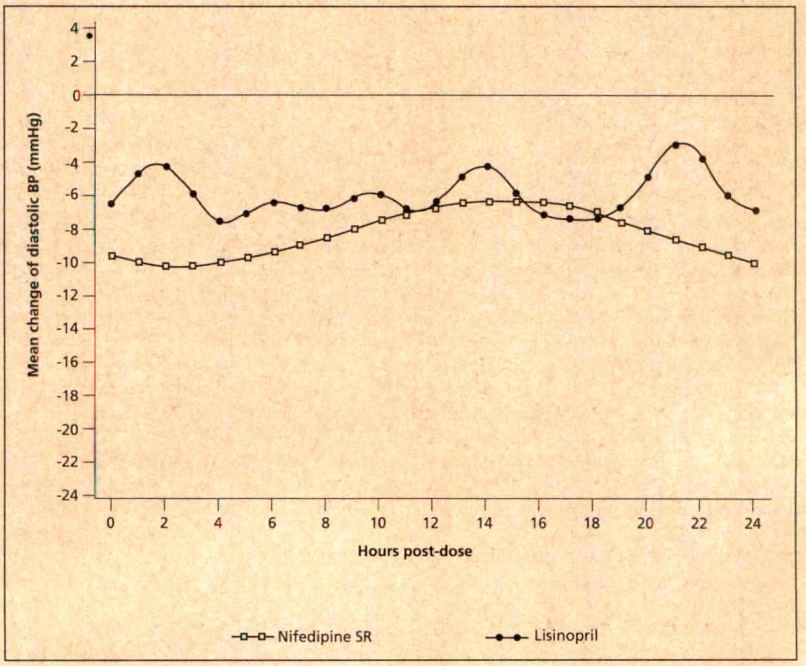


FIGURE 1. Effects of nifedipine SR and lisinopril on diastolic blood pressure, recorded with a 24-hour ambulatory monitoring device (after 8 weeks of treatment).

characteristics and comorbid illnesses of the patient. Other important factors are the drug's regimen and daily dosage, which may determine compliance, and the adverse effect profile of the drug.

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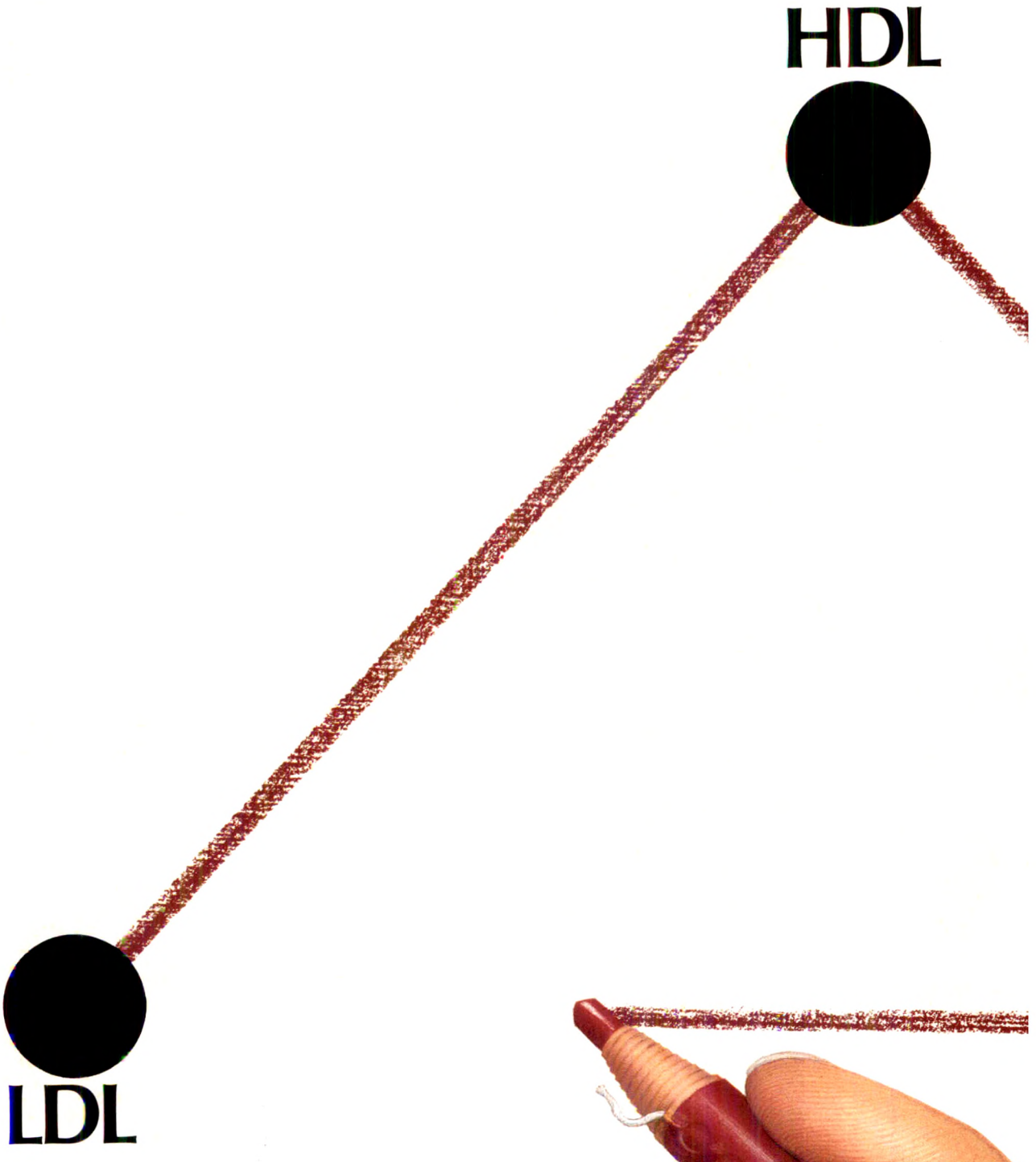
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Make this connection to reduce heart attack risk

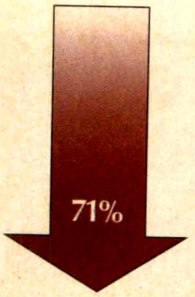


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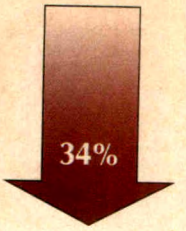
To reduce heart attack risk, don't overlook coexisting low HDL, high triglycerides, and high LDL. A recently published analysis of data from a Helsinki Heart Study subgroup shows why:

LOPID reduced the incidence of heart attack* 71%

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—in a high-risk subgroup of patients with multiple lipid disorders. While the overall reduction in heart attack was 34%, the greatest reduction in heart attack was achieved among those LOPID patients with baseline triglycerides >200 mg/dL and baseline LDL/HDL >5 (n = 154).†[1]



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BID

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TREATS THE ENTIRE TRIAD DRAMATICALLY REDUCES HEART ATTACK

LOPID is indicated for reducing the risk of coronary heart disease in type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid. LOPID is not indicated for the treatment of patients with low HDL as their only lipid abnormality.

Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

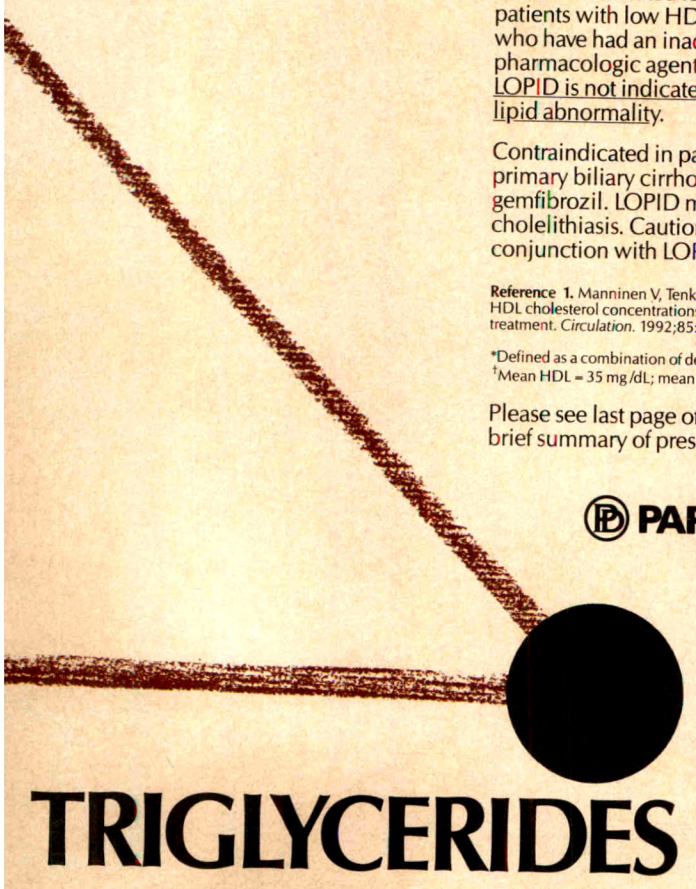
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*Defined as a combination of definite coronary death and/or definite myocardial infarction.
†Mean HDL = 35 mg/dL; mean LDL = 208 mg/dL; $P = .005$; 95% CI 21.2 to 118.6.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

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Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

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RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
DRAMATICALLY REDUCES HEART ATTACK

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

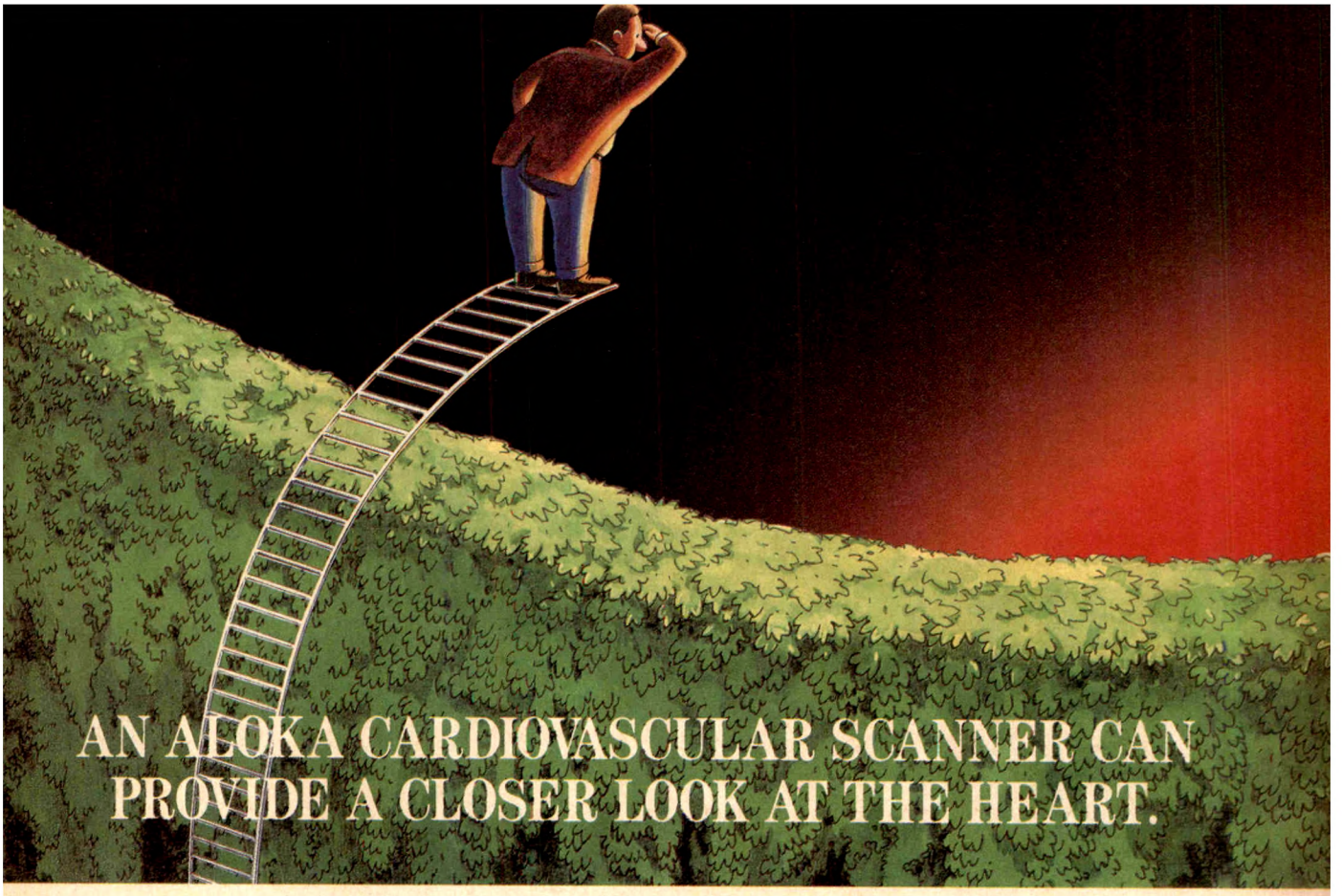
MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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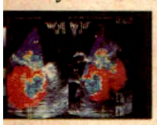
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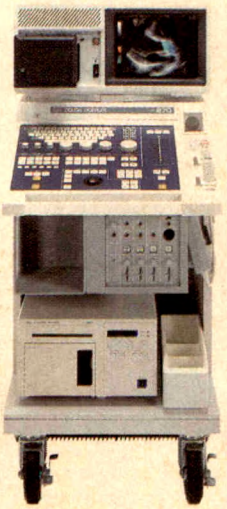
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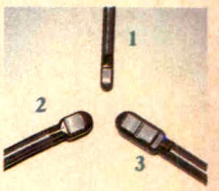
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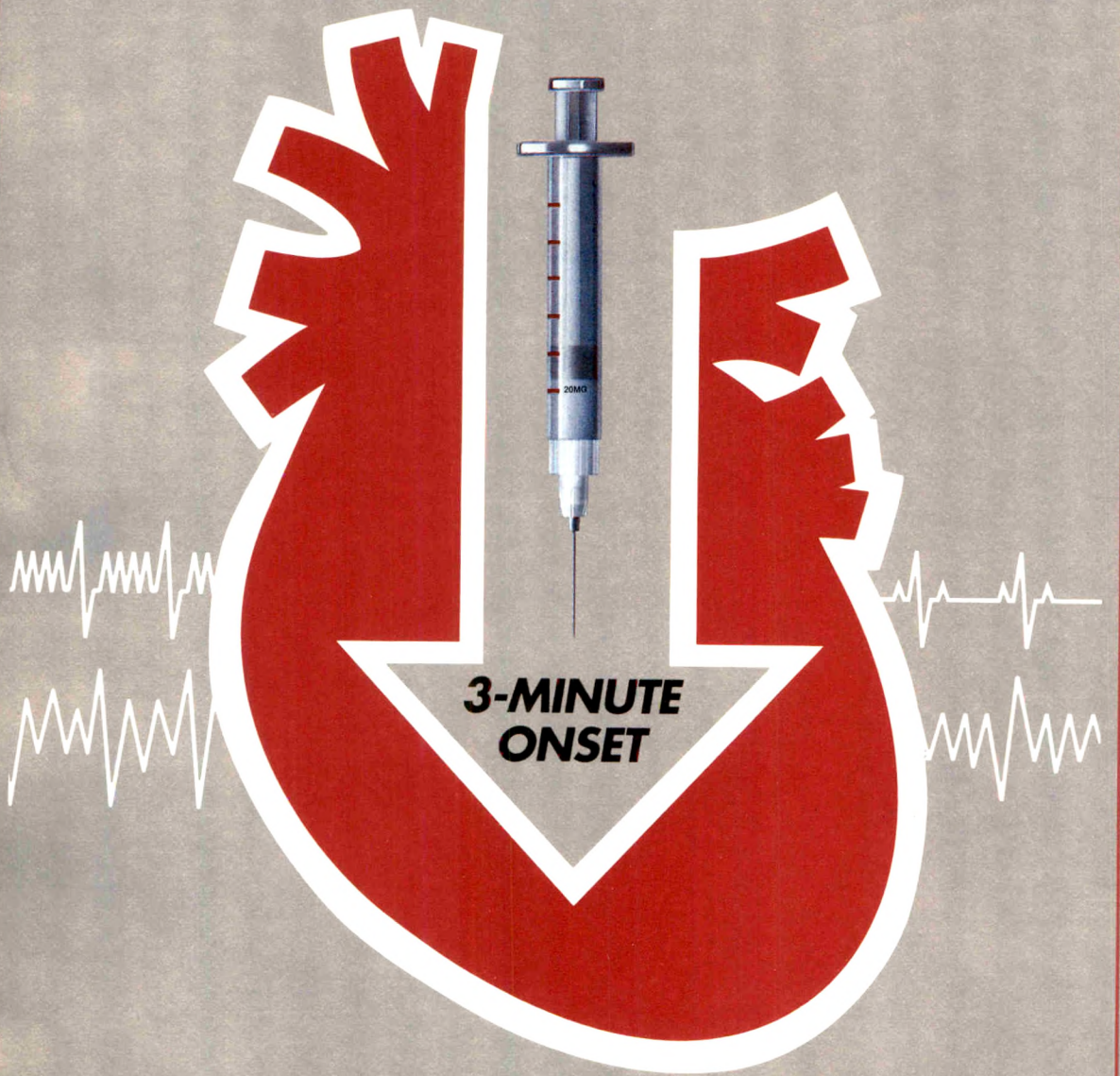
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(diltiazem hydrochloride)
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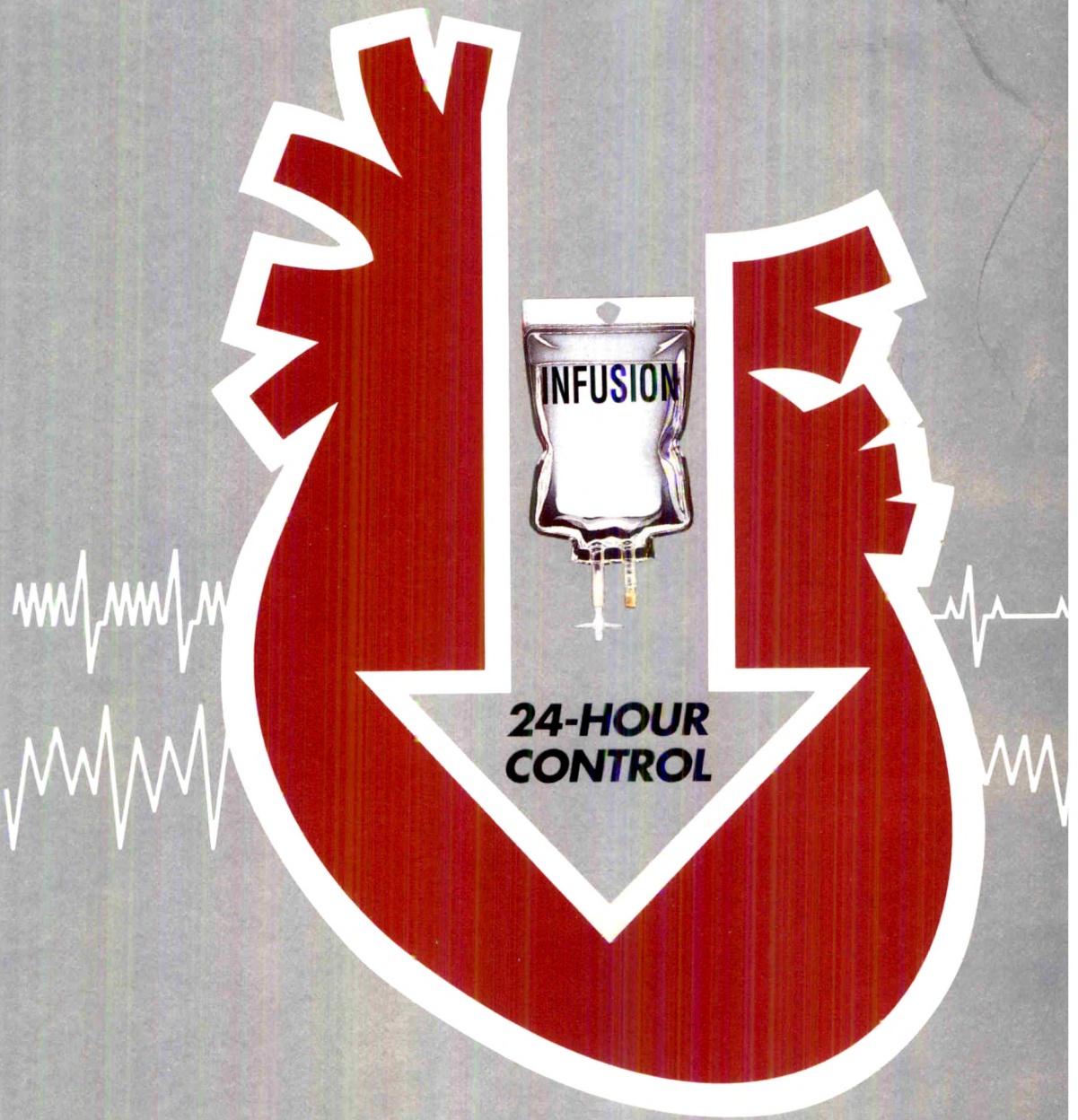
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CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS | INFUSION



Should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

CIVAG800/A6120

For heart rate control during atrial fibrillation and flutter

MAINTAINS HEART RATE CONTROL SAFELY

FAST

- 3-minute onset of action following bolus injection[1]
- 95% response rate within 2 to 7 minutes of administration[1]
- 1- to 3-hour duration of action with initial bolus

SAFE

- 4.3% incidence of asymptomatic hypotension[1]*
- 3.2% incidence of symptomatic hypotension[1]*
- 3.9% incidence of injection site reaction[1]
- 1.7% incidence of flushing[1]*
- Little negative inotropic effect[1†]
- Do not use in patients with WPW or short PR syndrome

  Other contraindications: sick sinus syndrome or second- or third-degree AV block, except with a functioning pacemaker; severe hypotension or shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

CONTINUOUS CONTROL

- Heart rate control through infusion for up to 24 hours[1, 2]

  Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

*Occurs most often during or immediately following bolus injection.
†Caution should be used in patients with congestive heart failure.

CARDIZEM INJECTABLE
Heart rate control that is fast, safe, and continuous

Please see brief summary of prescribing information on next page.

0154B2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION

CONVENIENT DOSAGE

1	2	3
Beginning treatment as	If response is inadequate, wait 15 minutes	Treatment as
BOLUS: 0.25 mg/kg actual body weight over 2 minutes	**BOLUS:** 0.35 mg/kg actual body weight over 2 minutes	**INFUSION: 10* to 15 mg/hr** *5 mg/hr may be appropriate starting infusion for some patients.
20 mg average patient	**25 mg average patient**	

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM (diltiazem hydrochloride) undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 24-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 10 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rate. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reaction (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

References: 1. Cardizem Injectable prescribing information. 2. Ellenbogen KA, Dias VC, Plumb VJ, Heywood JT, Mirvis DM. *J Am Coll Cardiol.* 1991;18:891-897.

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The American Journal of Cardiology®

MAY 1, 1992, VOL. 69, NO. 14

CORONARY ARTERY DISEASE

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MAY 1, 1992, VOL. 69, NO. 14

CORONARY ARTERY DISEASE

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Importance of a Patent Infarct-Related Artery for Hospital and Late Survival After Direct Coronary Angioplasty for Acute Myocardial Infarction

Bruce R. Brodie, Thomas D. Stuckey, Charles J. Hansen, Terry R. Cooper, Richard A. Weintraub, E. Joseph LeBauer, Jeffrey D. Katz, and Thomas A. Kelly

The importance of a patent infarct-related artery (IRA) on hospital and late survival was examined in 383 patients with acute myocardial infarction treated with direct coronary angioplasty. Patency of the IRA was the most important determinant of hospital survival, and left ventricular (LV) function (measured after recovery) was the most important determinant of late cardiac survival. Patency was not a predictor of late cardiac survival in the group of hospital survivors as a whole, but was important for late survival in patients with depressed initial LV function. Patients with patent arteries had substantial recovery of LV function, whereas patients with occluded arteries did not. When late cardiac survival was adjusted for differences in recovered LV function, patency was no longer a predictor of late cardiac survival in the subgroup of patients with depressed initial LV function. Our results indicate that patency of the IRA is important for hospital survival and for preservation of LV function, but is not an independent determinant of late cardiac survival.

1120

Evaluation of a Prolonged Infusion of Recombinant Tissue-Type Plasminogen Activator (Duteplase) in Preventing Reocclusion Following Successful Thrombolysis in Acute Myocardial Infarction

John Kalbfleisch, Udho Thadani, Judith K. LittleJohn, Greg Brown, Raymond Magorien, Michael Kutcher, George Taylor, William T. Maddox, W. Barton Campbell, James Perry, Jr., James F. Spann, George Vetrovec, Richard Kent, and Paul W. Armstrong

The hypothesis that an infusion of recombinant tissue-type plasminogen activator (rt-PA) maintained for up to 24 hours could prevent reocclusion after early coronary patency had been established was evaluated in acute myocardial infarction. Coronary patency was documented in 139 of 213 patients who had a 90-minute angiogram recorded after an initial lytic dose of rt-PA (Duteplase®, Burroughs Wellcome Co.) administered ac-

Continued on page A16

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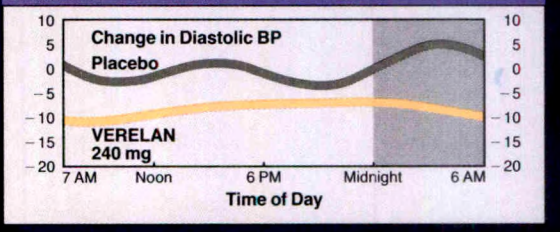
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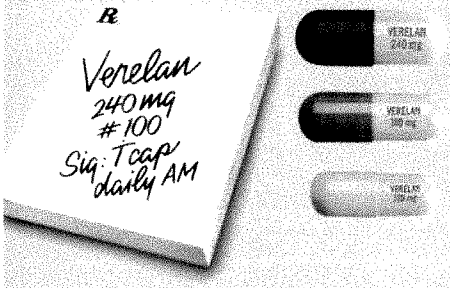
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eferences: 1. Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-mod-rate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol.* 1991;31:144-50. **2.** Data on file for VERELAN 240 mg, Lederle Laboratories, Pearl River, NY.

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LINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release ERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter r atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **/ARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 6 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to bout 30% of normal.

:ONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic hock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker s present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **/ARNINGS**), hypersensitivity to verapamil.

/ARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before /ERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can

VERELAN® verapamil HCl

increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%), dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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8. ibid.

cording to body weight. Patients (16.5%) had reocclusion after repeat angiography 9 to 21 hours after a maintenance infusion of rt-PA continued for 9 to 21 hours. No significant relationship was evident between the maintenance dose rate and incidence of reocclusion, but a strong association was seen between total dose of rt-PA and the incidence (16%) of serious or life-threatening bleeding. Repeat thrombosis after establishment of early patency after rt-PA remains a significant problem and is unaffected by sustained rt-PA infusion in doses that can be tolerated.

1128

Differential Long-Term Impact of In-Hospital Symptoms of Psychological Stress After Non-Q-Wave and Q-Wave Acute Myocardial Infarction

Nancy Frasure-Smith, François Lespérance, and Martin Juneau

It was hypothesized that patients with non-Q-wave acute myocardial infarction (AMI) are more vulnerable to the effects of psychological stress than are Q-wave patients and thus would be more likely to benefit from stress relief. A standardized index of psychological stress symptoms was administered to 461 men hospitalized for AMI. After discharge they took part in a 1-year randomized clinical trial of psychological stress monitoring and intervention. Among patients with non-Q-wave AMI receiving usual care, a high level of stress symptoms in hospital was associated with a more than fivefold increase in the relative risk of cardiac mortality over the first year after infarct ($p = 0.01$). Patients with Q-wave AMI in the control group had no stress-related increase in risk. In the treatment group, high stress had no impact on cardiac mortality regardless of the type of AMI. In conclusion, the prognostic impact of psychological stress is more apparent among patients with non-Q-wave than Q-wave AMI, and stress-relieving interventions may be of particular importance for them.

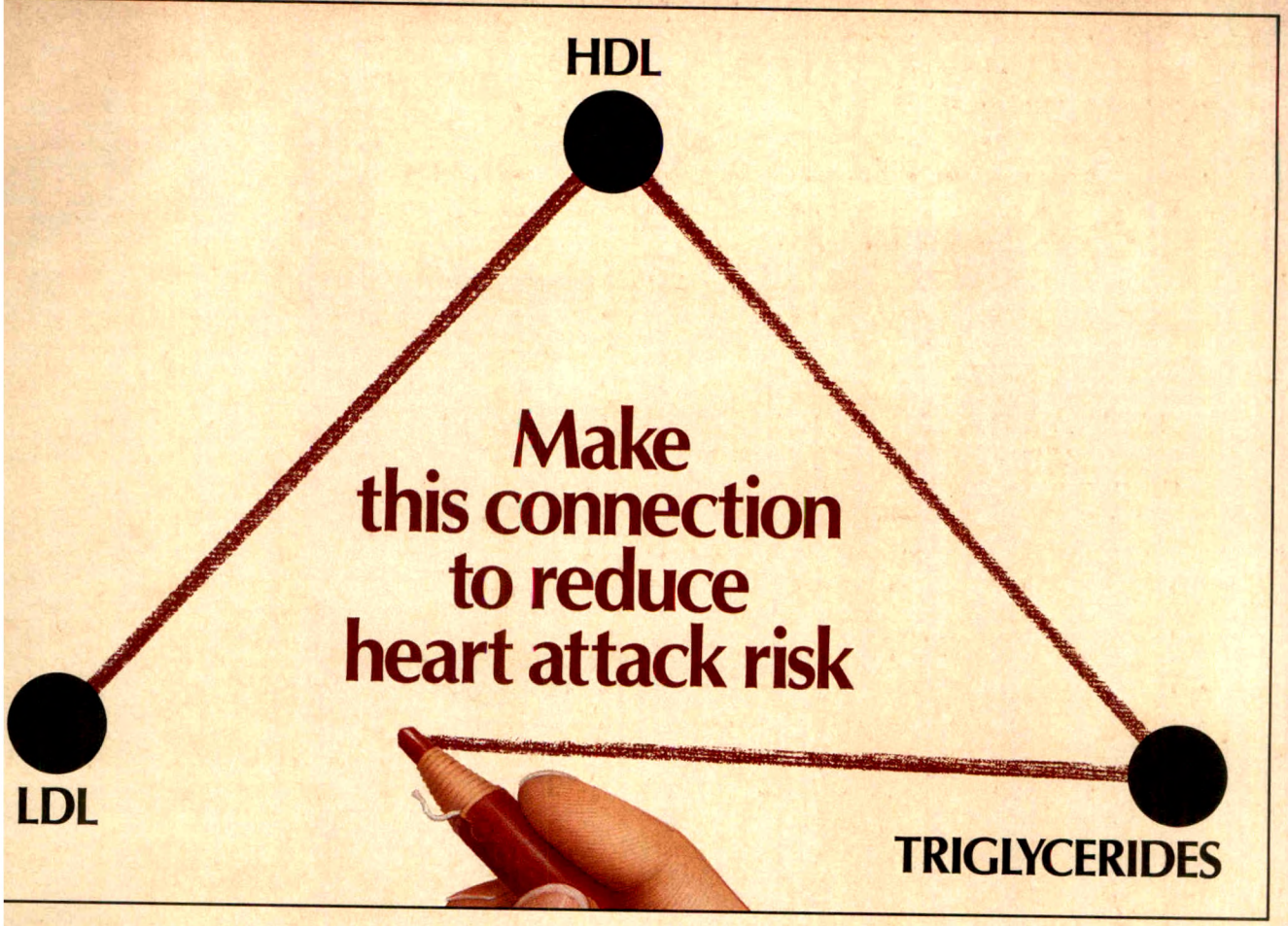
1135

Prognosis of Acute Myocardial Infarction Complicated by Complete Heart Block (the Worcester Heart Attack Study)

Robert J. Goldberg, Juan C. Zevallos, Jorge Yarzebski, Joseph S. Alpert, Joel M. Gore, Zuoyao Chen, and James E. Dalen

As part of a community-based study of patients hospitalized with acute myocardial infarction (AMI), changes over time in the incidence and survival rates of complete heart block (CHB) complicating AMI and of its prognostic impact were examined. The incidence rates of CHB remained relatively stable at 5.8% over the time period (1975 to 1988) studied. The incidence rates of CHB were approximately twice as high in AMI patients with inferior/posterior as in those with anterior wall AMI. Patients with AMI developing CHB had higher in-hospital fatality rates than did those without CHB. The in-hospital survival associated with CHB did not improve over time. Long-term survival rates for up to a 14-year follow-up period for discharged surviving patients were not significantly different for AMI patients with compared with those without CHB.

Continued on page A21



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—in a high-risk subgroup of Helsinki Heart Study (HHS) patients with a triad of lipid disorders: coexisting low HDL, high triglycerides, and high LDL. While the overall reduction in heart attack in the HHS was 34%, the greatest reduction was achieved among these LOPID patients with baseline triglycerides >200 mg/dL and baseline LDL/HDL ratio >5 (n = 154).†[1]

TREATS THE ENTIRE TRIAD DRAMATICALLY REDUCES HEART ATTACK

ID is indicated for reducing the risk of coronary heart ase in type IIb patients with low HDL, in addition to ated LDL and triglycerides, and who have had an equate response to weight loss, diet, exercise, and other macologic agents such as bile acid sequestrants and inic acid. LOPID is not indicated for the treatment of nts with low HDL as their only lipid abnormality.

ed as a combination of definite coronary death and/or definite myocardial infarction.

HDL = 35 mg/dL; mean LDL = 208 mg/dL; $P = .005$; 95% CI 21.2 to 118.6.

nce 1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride L cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the i Heart Study: implications for treatment. *Circulation.* 1992;85:37-45.

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Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anticoagulants are given in conjunction with LOPID.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.

PARKE-DAVIS

BOOTS PHARMACEUTICALS

Lopid® (Gemfibrozil Capsules and Tablets)

Before prescribing, please see full prescribing information.
A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

Lopid® (Gemfibrozil Capsules and Tablets)

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

LOPID® Lopid BID
(gemfibrozil) 600-mg Tablets
RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
DRAMATICALLY REDUCES HEART ATTACK

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J. B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

Caution—Federal law prohibits dispensing without prescription.

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

0737G013
PD-56-JA-7731-A1(032

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

ONE TO SWITCH TO

Easy to switch from Cardizem® SR (diltiazem HCl) **on a total mg/day basis**

Convenient once-a-day dosage for proven 24-hour control[1]

A favorable side-effect profile[1]

Once-a-day dosing schedules result in improved compliance[2]

LOWER PRICE*

20% lower cost than Cardizem® SR capsules

Flexible dosage range

- Start with one 180-mg capsule daily
- Available in 180-, 240-, and 300-mg dosage strengths

*Based on AWP prices.

Cardizem CD is indicated for the treatment of hypertension.

Please see brief summary of prescribing information on next page.

ONCE A DAY

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

MARION MERRELL DOW INC.
PRESCRIPTION PRODUCTS DIVISION
KANSAS CITY, MO 64114

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7227T1

ONCE A DAY

NEW

ONCE-A-DAY CARDIZEM® CD

(diltiazem HCl)

Switch from Cardizem® SR on a total mg/day basis

For new patients starting on Cardizem® CD:

- Start with one 180-mg capsule daily
- Monitor for 2 weeks; if optimal response is not met
- Titrate to goal blood pressure

BRIEF SUMMARY

CARDIZEM® CD (diltiazem hydrochloride) Capsules

CARDIZEM® SR (diltiazem hydrochloride) Sustained Release Capsules

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS

1. Cardiac Conduction. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (13 of 3,007 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.

2. Congestive Heart Failure. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% ± 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Worsening of congestive heart failure has been reported in patients with preexisting impairment of ventricular function. Experience with the use of CARDIZEM in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

3. Hypotension. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.

4. Acute Hepatic Injury. Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.) Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs such as cyclosporin, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either CARDIZEM Tablets or CARDIZEM SR Capsules as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients taking CARDIZEM Tablets or CARDIZEM SR Capsules studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first-degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related.

DOUBLE BLIND PLACEBO CONTROLLED HYPERTENSION TRIALS

ADVERSE	DILTIAZEM N=315 # PTS (%)	PLACEBO N=211 # PTS (%)
Headache	38 (12%)	17 (8%)
AV Block First Degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG Abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk Phos Increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV Block Second Degree	2 (0.6%)	—

The following table presents the most common adverse reactions reported in placebo-controlled trials in patients receiving CARDIZEM CD up to 360 mg with rates in placebo patients shown for comparison.

ADVERSE REACTION	CARDIZEM CD N=324	PLACEBO N=175
HEADACHE	9.0%	8.0%
BRADYCARDIA	4.3%	2.3%
EDEMA	3.7%	2.3%
DIZZINESS	3.1%	3.4%
ECG ABNORMALITY	3.1%	2.9%
AV BLOCK FIRST DEGREE	2.2%	—
ASTHENIA	1.9%	1.7%

In clinical trials of CARDIZEM CD Capsules, CARDIZEM Tablets, and CARDIZEM SR Capsules involving over 3000 patients, the most common events (ie, greater than 1%) were edema (4.9%), headache (4.9%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.2%), bradycardia (1.6%), flushing (1.5%), nausea (1.4%), rash (1.3%), and dyspepsia (1.2%).

In addition, the following events were reported infrequently (less than 1%).

Cardiovascular: Angina, arrhythmia, AV block (second- or third-degree), bundle branch block, congestive heart failure, ECG abnormalities, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

HOW SUPPLIED

CARDIZEM® CD (diltiazem hydrochloride) is available as capsules of 180 mg, 240 mg, and 300 mg in bottles of 30 and 90, and in UDIP® packages of 100.

CARDIZEM® SR (diltiazem hydrochloride) is available as sustained release capsules of 60 mg, 90 mg, and 120 mg in bottles of 100, and in UDIP® packages of 100.

Product Information as of October 1991

References: **1.** Data on file, Marion Merrell Dow Inc. **2.** Cramer JA, Mattson RH, Prevey ML, et al. JAMA. 1989;261(22):3273-3274.

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KANSAS CITY, MO 64114

1143

Effect of Spinal Cord Stimulation on Regional Myocardial Perfusion Assessed by Positron Emission Tomography

Christian De Landsheere, Clas Mannheimer, Alfons Habets, Marcel Guillaume, Ivan Bourgeois, Lars-Erik Augustinsson, Tore Eliasson, Daniel Lamotte, Henri Kulbertus, and Pierre Rigo

Spinal cord stimulation (SCS) can relieve symptoms in patients with severe angina pectoris refractory to conventional medical or surgical therapy. Positron emission tomography and potassium-38 were used in 8 patients for the quantitative evaluation of regional myocardial perfusion at rest and after exercise, before and during SCS. In nonaffected segments, regional myocardial clearance (flow × extraction) of potassium-38 increased from rest to exercise before and after SCS. In affected segments, no changes were observed in the exercise regional myocardial clearance after SCS, although a small difference was observed at rest concomitant with an increased heart rate. Anginal pain as well as the magnitude and duration of ST-segment depression was attenuated in all but 1 patient. These results indicate that SCS improves exercise-induced angina and electrocardiographic signs of ischemia, but this influence does not appear to be mediated by changes in regional myocardial perfusion.

1150

Usefulness of Single-Photon Emission Computed Tomography of Thallium-201 Uptake After Dipyridamole Infusion for Detection of Coronary Artery Disease

Marla A. Mendelson, Stewart M. Spies, William G. Spies, Pierre Abi-Mansour, and Dan J. Fintel

The diagnostic performance of single-photon emission computed tomography (SPECT) and planar imaging of thallium-201 uptake for the detection of coronary artery disease (CAD) was compared in 79 patients who underwent both dipyridamole thallium-201 scintigraphy and coronary angiography. The overall detection of CAD was 89% for SPECT and 67% for planar imaging ($p < 0.001$). For the anterior vascular territory, sensitivities for SPECT and planar imaging were 69 and 44% ($p < 0.01$), respectively; for the posterior vascular territory, sensitivities were 80 and 54% ($p < 0.01$), respectively. Receiver-operating characteristic analysis, using a 5-point evaluation scale, was performed for the anterior and posterior vascular territories. Receiver-operating characteristic curves generated for SPECT and planar studies demonstrated improved diagnostic performance by SPECT in the anterior vascular territory, but showed similar performance in the posterior territory because of lower SPECT specificity despite higher sensitivity at clinically relevant decision thresholds. Thus, SPECT thallium-201 scintigraphy is an important and necessary clinical tool in the detection of CAD after dipyridamole infusion.



Continued on page A24

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1156

Efficacy of a Single Dose of Slow-Release Isosorbide Dinitrate in the Treatment of Silent or Painful Myocardial Ischemia in Stable Angina Pectoris

Jerzy P. Dubiel, Krzysztof W. Moczurad, and Leszek Bryniarski

A double-blind study was conducted in 32 patients with stable angina pectoris to determine the effect of a single dose of 120 mg of slow-release isosorbide dinitrate versus placebo on the incidence of silent and painful ischemic episodes as assessed by exercise treadmill testing and 48-hour ambulatory electrocardiographic monitoring. Assessments were obtained at baseline and repeated at 20 and 21 days of the drug or placebo administration. Slow-release isosorbide dinitrate (a single dose of 120 mg/day) is a valuable drug for stable angina pectoris, decreasing the frequency of silent and painful ischemic episodes and the magnitude of ST-segment depressions, and increasing exercise tolerance. It particularly shortened the duration of silent episodes.

1161

Comparison of Results of Percutaneous Transluminal Coronary Angioplasty With and Without Selective Requirement of Surgical Standby

Andrés Iñiguez, Carlos Macaya, Rosana Hernandez, Fernando Alfonso, Javier Goicolea, Jorge Casado, and Pedro Zarco

The outcomes of 269 percutaneous transluminal coronary angioplasties (PTCA) with rigorous surgical standby (patients considered at high risk should acute vessel closure occur) and of 1,014 PTCAs without surgical standby (although the surgical team was in-house) (backup group) were analyzed. In the group with surgical standby, dilatation was more frequently multiple, performed in the left anterior descending coronary artery, in bypass graft lesions, in proximal coronary segments and in lesions at bifurcation, and less frequently performed during the same diagnostic procedure. Angiographic success was achieved in 91 and 92% of the attempted lesions and PTCA success in 89 and 88% in the standby and backup groups, respectively. The occurrence of death (1 vs 0.7%), acute myocardial infarction (2.9 vs 2.7%) or emergency surgery (0.7 vs 0.1%) was similar in both groups. PTCA is a safe procedure with a relatively low incidence of complications, independent of the surgical coverage used. A rigorous standby surgery is not necessary in every case, and criteria able to better select higher risk patients who will require a rigorous surgical coverage are still needed.

1166

Frequency and Prognostic Significance of Silent Coronary Artery Disease in Patients with Cerebral Ischemia Undergoing Carotid Endarterectomy

Stefano Urbinati, Giuseppe Di Pasquale, Alvaro Andreoli, Anna Maria Lusa, Michele Ruffini, Giuseppe Lanzino, and Giuseppe Pinelli

The prevalence and prognostic role of silent coronary artery disease (CAD) was investigated in 106 patients undergoing carotid endarterectomy with neither history nor electrocardiographic signs of CAD. Patients were stratified as to the presence or absence of silent CAD defined by

Continued on page A30

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HE WORD FOR ALL THE BENEFITS OF THROMBOLYTIC THERAPY

Low incidence of ICB (0.5%)[1-9] when used with IV heparin

B rates in clinical trials with Activase® and IV heparin[1-9]

inical source	N	% ICB	Reported occurrence (n)
MI-II*[1]	3,016	0.4%	13
oled data from other studies**[2-9]	3,359	0.6%	19
tal	6,375	0.5%	32

the TIMI-II (Thrombolysis in Myocardial Infarction) study, the gest U.S. thrombolytic trial to date, 3,016 patients were treated th IV heparin, aspirin, and 100 mg of Activase®; the occurrence intracranial hemorrhage was 0.4%.[1]

A cumulative mortality rate of 5.9%[2,10] for a positive effect on survival

inical source	N	% mortality	Reported deaths (n)
SET†[2]	2,515	7.2%	182
MI-II*[10]	3,016	4.8%	146
tal	5,531	5.9%	328

reported ICB occurrence in ASSET trial (n=2,515)
rin was not used in the ASSET trial

Bleeding is the most common complication of thrombolytic therapy, with intracranial bleeding being the most serious. Activase® is contraindicated in patients with: active internal bleeding, history of cerebrovascular accident, recent (within two months) intracranial or intraspinal surgery or trauma, intracranial neoplasm, arteriovenous malformation or aneurysm, known bleeding diathesis, or severe uncontrolled hypertension. (See WARNINGS section of prescribing information.)

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ef Summary
nsult full prescribing information before using.

DICATIONS AND USAGE: ACTIVASE® is indicated for use in the management of acute myocardial arction (AMI) in adults for the lysis of thrombi obstructing coronary arteries, the reduction of infarct e, the improvement of ventricular function following AMI, the reduction of the incidence of congesheart failure and the reduction of mortality associated with AMI. Treatment should be initiated as on as possible after the onset of AMI symptoms.
TIVASE® is also indicated in the management of acute massive pulmonary embolism (PE) in ults: for the lysis of acute pulmonary emboli, defined as obstruction of blood flow to a lobe or ltiple segments of the lungs, and for the lysis of pulmonary emboli accompanied by unstable modynamics, i.e., failure to maintain blood pressure without supportive measures. The diagnosis ould be confirmed by objective means, such as pulmonary angiography or noninvasive procedures such lung scanning.
NTRAINDICATIONS: Because thrombolytic therapy increases the risk of bleeding, ACTIVASE® contraindicated in the following situations: • Active internal bleeding • History of cerebrovasar accident • Recent (within two months) intracranial or intraspinal surgery or trauma (see ARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding thesis • Severe uncontrolled hypertension.
ARNINGS: Bleeding The most common complication encountered during ACTIVASE® therapy is eding. The type of bleeding associated with thrombolytic therapy can be divided into two broad egories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or racranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., es of venous cutdown, arterial puncture, recent surgical intervention).
Concomitant use of heparin anticoagulation may contribute to bleeding. Some hemorrhagic episodes curred one or more days after the effects of ACTIVASE® had dissipated, but while heparin therapy s continuing.
As fibrin is lysed during ACTIVASE® therapy, bleeding from recent puncture sites may occur. erefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including sites catheter insertion, arterial and venous puncture, cutdown and needle puncture).
ntramuscular injections and nonessential handling of the patient should be avoided during treatment h ACTIVASE®. Venipunctures should be performed carefully and only as required.
Should an arterial puncture be necessary during an infusion of ACTIVASE®, it is preferable to use an per extremity vessel accessible to manual compression. Pressure should be applied for at least 30 utes, a pressure dressing applied and the puncture site checked frequently for evidence of bleeding. Should serious bleeding (not controllable by local pressure) occur, the infusion of ACTIVASE® and concomitant heparin should be terminated immediately.
ach patient being considered for therapy with ACTIVASE® should be carefully evaluated and anticied benefits weighed against potential risks associated with therapy.
n the following conditions, the risks of ACTIVASE® therapy may be increased and should be weighed inst the anticipated benefits: • Recent (within 10 days) major surgery, e.g., coronary artery bypass ft, obstetrical delivery, organ biopsy, previous puncture of noncompressible vessels • Cerebrovasar disease • Recent (within 10 days) gastrointestinal or genitourinary bleeding • Recent (within 10 s) trauma • Hypertension: systolic BP≥180 mm Hg and/or diastolic BP≥110 mm Hg • High lihood of left heart thrombus, e.g., mitral stenosis with atrial fibrillation • Acute pericarditis • bacute bacterial endocarditis • Hemostatic defects including those secondary to severe hepatic or al disease • Significant liver dysfunction • Pregnancy • Diabetic hemorrhagic retinopathy, or other morrhagic ophthalmic conditions • Septic thrombophlebitis or occluded AV cannula at seriously cted site • Advanced age, i.e., over 75 years old • Patients currently receiving oral anticoagulants • other condition in which bleeding constitutes a significant hazard or would be particularly icult to manage because of its location.
hythmias Coronary thrombolysis may result in arrhythmias associated with reperfusion. These hythmias are not different from those often seen in the ordinary course of AMI and may be managed h standard antiarrhythmic measures. It is recommended that antiarrhythmic therapy for bradycardia /or ventricular irritability be available when infusions of ACTIVASE® are administered.
monary Embolism It should be recognized that the treatment of pulmonary embolism with TIVASE®, Alteplase, has not been shown to constitute adequate clinical treatment of underlying p vein thrombosis. Furthermore, the possible risk of reembolization due to the lysis of underlying p venous thrombi should be considered.
ECAUTIONS: General Standard management of myocardial infarction or pulmonary embolism uld be implemented concomitantly with ACTIVASE® treatment. Noncompressible arterial punc must be avoided. Arterial and venous punctures should be minimized. In the event of serious eding, ACTIVASE® and heparin should be discontinued immediately. Heparin effects can be ersed by protamine.
dministration There is no experience with readministration of ACTIVASE®. If anaphylactoid reaction urs, infusion should be discontinued immediately and appropriate therapy initiated.
lthough sustained antibody formation in patients receiving one dose of ACTIVASE® has not been umented, readministration should be undertaken with caution.
oratory Tests During ACTIVASE® therapy, results of coagulation tests and/or measures of fibrino activity may be unreliable unless specific precautions are taken to prevent *in vitro* artifacts. TIVASE® is an enzyme that when present in blood in pharmacologic concentrations remains active er *in vitro* conditions. This can lead to degradation of fibrinogen in blood samples removed for lysis. Collection of blood samples in the presence of aprotinin (150-200 units/mL) can to some nt mitigate this phenomenon.
g Interactions The interaction of ACTIVASE® with other cardioactive drugs has not been studied. In tion to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function h as acetylsalicylic acid, dipyridamole) may increase the risk of bleeding if administered prior to, ng or after ACTIVASE® therapy.
of Anticoagulants Heparin has been administered concomitantly with and following infusions of IVASE® to reduce the risk of rethrombosis. Because either heparin or ACTIVASE® alone may cause ding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.
gnancy (Category C) Animal reproduction studies have not been conducted with ACTIVASE®. It is not known whether ACTIVASE® can cause fetal harm when administered to a pregnant woman can affect reproduction capacity. ACTIVASE® should be given to a pregnant woman only if rly needed.
iatric Use Safety and effectiveness of ACTIVASE® in children has not been established.
cinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have not been formed to evaluate the carcinogenic potential or the effect on fertility. Short-term studies, which luated tumorigenicity of ACTIVASE® and effect on tumor metastases in rodents, were negative.
tudies to determine mutagenicity (Ames test) and chromosomal aberration assays in human phocytes were negative at all concentrations tested. Cytotoxicity, as reflected by a decrease nitotic index, was evidenced only after prolonged exposure and only at the highest concentrais tested.
sing Mothers It is not known whether ACTIVASE® is excreted in human milk. Because many gs are excreted in human milk, caution should be exercised when ACTIVASE® is administered to a sing woman.

ADVERSE REACTIONS: Bleeding The most frequent adverse reaction associated with ACTIVASE® is bleeding. The type of bleeding associated with thrombolytic therapy can be divided into two broad categories: • Internal bleeding involving the gastrointestinal or genitourinary tract, or retroperitoneal or intracranial sites • Superficial or surface bleeding, observed mainly at invaded or disturbed sites (e.g., sites of venous cutdown, arterial puncture, recent surgical intervention).

The following incidence of significant internal bleeding (estimated as >250 cc blood loss) has been reported in studies in over 800 patients treated at all doses:

	Total Dose ≤ 100 mg	Total Dose > 100 mg
gastrointestinal	5%	5%
genitourinary	4%	4%
ecchymosis	1%	<1%
retroperitoneal	<1%	<1%
epistaxis	<1%	<1%
gingival	<1%	<1%

The incidence of intracranial bleeding in patients treated with ACTIVASE®, Alteplase, recombinant, is as follows:

Dose	Number of Patients	%
100 mg	3272	0.4
150 mg	1779	1.3
1-1.4 mg/kg	237	0.4

These data indicate that a dose of 150 mg of ACTIVASE® should not be used because it has been associated with an increase in intracranial bleeding.

Recent data indicate that the incidence of stroke in 6 randomized double-blind placebo controlled trials[1-7] is not signficantly different in the ACTIVASE® treated patients compared to those treated with placebo (37/3161, 1.2% versus 27/3092, 0.9%, respectively) (p = 0.26).

Should serious bleeding in a critical location (intracranial, gastrointestinal, retroperitoneal, pericardial) occur, ACTIVASE® therapy should be discontinued immediately, along with any concomitant therapy with heparin.

Fibrin, which is part of the hemostatic plug formed at needle puncture sites, will be lysed during ACTIVASE® therapy. Therefore, ACTIVASE® therapy requires careful attention to potential bleeding sites.

Allergic Reactions No serious or life-threatening allergic reactions have been reported. Other mild hypersensitivity reactions such as urticaria have been observed occasionally.

Other Adverse Reactions Other adverse reactions have been reported, principally nausea and/or vomiting, hypotension, and fever. These reactions are frequent sequelae of MI and may or may not be attributable to ACTIVASE® therapy.

DOSAGE AND ADMINISTRATION: ACTIVASE® is for intravenous administration only. **ACUTE MYOCARDIAL INFARCTION: Administer ACTIVASE® as soon as possible after the onset of symptoms.**

The recommended dose is 100 mg administered as 60 mg (34.8 million IU) in the first hour (of which 6 to 10 mg is administered as a bolus over the first 1-2 minutes), 20 mg (11.6 million IU) over the second hour, and 20 mg (11.6 million IU) over the third hour. For smaller patients (less than 65 kg), a dose of 1.25 mg/kg administered over 3 hours, as described above, may be used.[8]

Although the use of anticoagulants and antiplatelet drugs during and following administration of ACTIVASE® has not been shown to be of unequivocal benefit, heparin has been administered concomitantly for 24 hours or longer in more than 90% of patients. Aspirin and/or dipyridamole have been given either during and/or following heparin treatment.

PULMONARY EMBOLISM: The recommended dose is 100 mg administered by intravenous infusion over two hours. Heparin therapy should be instituted or reinstituted near the end of or immediately following the ACTIVASE® infusion when the partial thromboplastin time or thrombin time returns to twice normal or less.

A DOSE OF 150 MG OF ACTIVASE® SHOULD NOT BE USED BECAUSE IT HAS BEEN ASSOCIATED WITH AN INCREASE IN INTRACRANIAL BLEEDING.

Reconstitution and Dilution DO NOT USE IF VACUUM IS NOT PRESENT.

ACTIVASE® should be reconstituted by aseptically adding the appropriate volume of the accompanying Sterile Water for Injection, USP to the vial. It is important that ACTIVASE® be reconstituted only with Sterile Water for Injection, USP, without preservatives. Do not use Bacteriostatic Water for Injection, USP. The reconstituted preparation results in a colorless to pale yellow transparent solution containing ACTIVASE® 1.0 mg/mL at approximately pH 7.3. The osmolality of this solution is approximately 215 mOsm/kg.

Because ACTIVASE® contains no antibacterial preservatives, it should be reconstituted immediately before use. The solution may be used for intravenous administration within 8 hours following reconstitution when stored between 2-30°C. Before further dilution or administration, the product should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

ACTIVASE® may be administered as reconstituted at 1.0 mg/mL. As an alternative, the reconstituted solution may be diluted further immediately before administration in an equal volume of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to yield a concentration of 0.5 mg/mL. Either polyvinyl chloride bags or glass bottles are acceptable. ACTIVASE® is stable for up to 8 hours in these solutions at room temperature. Exposure to light has no effect on the stability of these solutions. Excessive agitation during dilution should be avoided; mixing should be accomplished with gentle swirling and/or slow inversion. Do not use other infusion solutions, e.g., Sterile Water for Injection, USP or preservative-containing solutions for further dilution.

No other medication should be added to infusion solutions containing ACTIVASE®. Any unused infusion solution should be discarded.

HOW SUPPLIED: ACTIVASE® is supplied as a sterile, lyophilized powder in 20 mg and 50 mg vials containing vacuum, each packaged with diluent for reconstitution.

Storage Store lyophilized ACTIVASE® at controlled room temperature not to exceed 30°C (86°F), or under refrigeration (2-8°C/36-46°F). Protect the lyophilized material during extended storage from excessive exposure to light.

Do not use beyond the expiration date stamped on the vial.

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concordant abnormal exercise electrocardiographic testing and thallium-201 myocardial scintigraphy. No deaths or cardiac events occurred in the perioperative period. During a mean follow-up of 5.4 years, 9 patients died (1.7%/year): fatal myocardial infarction occurred in 5 patients (all in silent CAD group). Nonfatal events were observed in 9 patients: cardiac in 4 (with silent CAD in 3). After 7 years, the Kaplan-Meier estimated survival free from coronary events was 51% in patients with and 98% in those without silent CAD ($p < 0.01$). In conclusion, silent CAD did not affect the perioperative prognosis, but strongly influenced the long-term follow-up. A systematic screening for silent CAD appears to be mandatory in all patients undergoing carotid endarterectomy.

1171

Coronary Vasodilatory Action of Elgodipine in Coronary Artery Disease

Harry Suryapranata, Athur Maas, Donald C. MacLeod, Pim J. de Feyter, Pieter D. Verdouw, and Patrick W. Serruys

The results of this study confirm for the first time the beneficial effects of elgodipine, a new second-generation dihydropyridine calcium antagonist, on systemic and coronary circulation in patients with coronary artery disease. Intravenous elgodipine at a rate of 1.5 μg/kg/min over a period of 10 minutes induced a marked decrease in systemic pressure, and a significant increase in coronary blood flow, but was free of observed cardiac depressant effect and did not influence heart rate or myocardial oxygen demand. Of particular relevance, elgodipine induced a significant vasodilation not only in nonstenotic but also in stenotic epicardial coronary arteries.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1178

Usefulness of Adenosine in Augmenting Ventricular Preexcitation for Noninvasive Localization of Accessory Pathways

Todd J. Cohen, Kelly J. Tucker, Joseph A. Abbott, Elias H. Botvinick, Elyse Foster, Nelson B. Schiller, J. William O'Connell, and Melvin M. Scheinman

Twelve-lead electrocardiograms and 2-dimensional echocardiograms were recorded at baseline and during adenosine-augmented ventricular preexcitation to better localize the accessory pathway. Echocardiograms were analyzed by direct inspection of digitized (16 frames per cycle) cine-loops and phase analysis. Phase analysis was performed on digitized 4-chamber and short-axis views, and transformed using a first harmonic Fourier algorithm. In 14 of 15 patients (93.3%), preexcitation became more prominent after adenosine, thus facilitating noninvasive pathway localization. Seven patients had no preexcitation at baseline, and in 4 of these patients, manifest preexcitation occurred after adenosine. Successful catheter ablation or electrophysiologic mapping of the accessory pathway location, or both, determined the accessory pathway location. In patients with preexcitation in response to adenosine, the electrocardiogram cor-

Continued on page A33

Introducing the

TENORMIN® (ATENOLOL) Wellspring SERVICE



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Please see adjacent page for brief summary of prescribing information.

TENORMIN® (atenolol) 25, 50, 100 mg tablets

(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT.)

INDICATIONS AND USAGE: Hypertension: TENORMIN is indicated in the management of hypertension. It may be used alone or concomitantly with other antihypertensive agents, particularly with a thiazide-type diuretic.

Angina Pectoris Due to Coronary Atherosclerosis: TENORMIN is indicated for the long-term management of patients with angina pectoris.

Acute Myocardial Infarction: TENORMIN is indicated in the management of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment can be initiated as soon as the patient's clinical condition allows. (See DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS.) In general, there is no basis for treating patients like those who were excluded from the ISIS-1 trial (blood pressure less than 100 mm Hg systolic, heart rate less than 50 bpm) or have other reasons to avoid beta blockade. As noted above, some subgroups (eg, elderly patients with systolic blood pressure below 120 mm Hg) seemed less likely to benefit.

CONTRAINDICATIONS: TENORMIN is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure. (See WARNINGS.)

WARNINGS: Cardiac Failure: Sympathetic stimulation is necessary in supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In patients who have congestive heart failure controlled by digitalis and/or diuretics, TENORMIN should be administered cautiously. Both digitalis and atenolol slow AV conduction.

In patients with acute myocardial infarction, cardiac failure which is not promptly and effectively controlled by 80 mg of intravenous furosemide or equivalent therapy is a contraindication to beta-blocker treatment.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic and the response observed closely. If cardiac failure continues despite adequate digitalization and diuresis, TENORMIN should be withdrawn. (See DOSAGE AND ADMINISTRATION.)

Cessation of Therapy with TENORMIN: Patients with coronary artery disease, who are being treated with TENORMIN, should be advised against abrupt discontinuation of therapy. Severe exacerbation of angina and the occurrence of myocardial infarction and ventricular arrhythmias have been reported in angina patients following the abrupt discontinuation of therapy with beta blockers. The last two complications may occur with or without preceding exacerbation of the angina pectoris. As with other beta blockers, when discontinuation of TENORMIN is planned, the patient should be carefully observed and advised to limit physical activity to a minimum. If the angina worsens or acute coronary insufficiency develops, it is recommended that TENORMIN be promptly reinstituted, at least temporarily. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TENORMIN therapy abruptly even in patients treated only for hypertension. (See DOSAGE AND ADMINISTRATION.)

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASE SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, TENORMIN may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, the lowest possible dose of TENORMIN should be used with therapy initiated at 50 mg and a beta$_2$-stimulating agent (bronchodilator) should be made available. If dosage must be increased, dividing the dose should be considered in order to achieve lower peak blood levels.

Anesthesia and Major Surgery: It is not advisable to withdraw beta-adrenoreceptor blocking drugs prior to surgery in the majority of patients. However, care should be taken when using anesthetic agents such as those which may depress the myocardium. Vagal dominance, if it occurs, may be corrected with atropine (1-2 mg IV).

Additionally, caution should be used when TENORMIN I.V. Injection is administered concomitantly with such agents.

TENORMIN, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects on the heart can be reversed by administration of such agents: eg, dobutamine or isoproterenol with caution (see section on OVERDOSAGE).

Diabetes and Hypoglycemia: TENORMIN should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. At recommended doses TENORMIN does not potentiate insulin-induced hypoglycemia and, unlike nonselective beta blockers, does not delay recovery of blood glucose to normal levels.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (eg, tachycardia) of hyperthyroidism. Patients suspected of having thyroid disease should be monitored closely when administering TENORMIN I.V. Injection. Abrupt withdrawal of beta blockade might precipitate a thyroid storm; therefore, patients suspected of developing thyrotoxicosis from whom TENORMIN therapy is to be withdrawn should be monitored closely. (See DOSAGE AND ADMINISTRATION.)

PRECAUTIONS: General: Patients already on a beta blocker must be evaluated carefully before TENORMIN is administered. Initial and subsequent TENORMIN dosages can be adjusted downward depending on clinical observations including pulse and blood pressure.

Impaired Renal Function: The drug should be used with caution in patients with impaired renal function. (SEE DOSAGE AND ADMINISTRATION.)

Drug Interactions: Catecholamine-depleting drugs (eg, reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with TENORMIN plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Should it be decided to discontinue therapy in patients receiving beta blockers and clonidine concurrently, the beta blocker should be discontinued several days before the gradual withdrawal of clonidine.

Caution should be exercised with TENORMIN I.V. Injection when given in close proximity with drugs that may also have a depressant effect on myocardial contractility. On rare occasions, concomitant use of intravenous beta blockers and intravenous verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure, or recent myocardial infarction.

Information on concurrent usage of atenolol and aspirin is limited. Data from several studies, ie, TIMI-II, ISIS-2, currently do not suggest any clinical interaction between aspirin and beta blockers in the acute myocardial infarction setting.

While taking beta blockers, patients with a history of anaphylactic reaction to a variety of allergens may have a more severe reaction on repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two long-term (maximum dosing duration of 18 or 24 months) rat studies and one long-term (maximum dosing duration of 18 months) mouse study, each employing dose levels as high as 300 mg/kg/day or 150 times the maximum recommended human antihypertensive dose,* did not indicate a carcinogenic potential of atenolol. A third (24 month) rat study, employing doses of 500 and 1,500 mg/kg/day (250 and 750 times the maximum recommended human antihypertensive dose*) resulted in increased incidences of benign adrenal medullary tumors in males and females, mammary fibroadenomas in females, and anterior pituitary adenomas and thyroid parafollicular cell carcinomas in males. No evidence of a mutagenic potential of atenolol was uncovered in the dominant lethal test (mouse), in vivo cytogenetics test (Chinese hamster) or Ames test (*S typhimurium*).

Fertility of male or female rats (evaluated at dose levels as high as 200 mg/kg/day or 100 times the maximum recommended human dose*) was unaffected by atenolol administration.

Animal Toxicology: Chronic studies employing oral atenolol performed in animals have revealed the occurrence of vacuolation of epithelial cells of Brunner's glands in the duodenum of both male and female dogs at all tested dose levels of atenolol (starting at 15 mg/kg/day or 7.5 times the maximum recommended human antihypertensive dose*) and increased incidence of atrial degeneration of hearts of male rats at 300 but not 150 mg atenolol/kg/day (150 and 75 times the maximum recommended human antihypertensive dose,* respectively).

Usage in Pregnancy: Pregnancy Category C: Atenolol has been shown to produce a dose-related increase in embryo/fetal resorptions in rats at doses equal to or greater than 50 mg/kg/day or 25 or more times the maximum recommended human antihypertensive dose.* Although similar effects were not seen in rabbits, the compound was not evaluated in rabbits at doses above 25 mg/kg/day or 12.5 times the maximum recommended human antihypertensive dose.* There are no adequate and well-controlled studies in pregnant women. TENORMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Based on the maximum dose of 100 mg/day in a 50 kg patient.

Nursing Mothers: Atenolol is excreted in human breast milk at a ratio of 1.5 to 6.8 when compared to the concentration in plasma. Caution should be exercised when TENORMIN is administered to a nursing woman. Clinically significant bradycardia has been reported in breast fed infants. Premature infants, or infants with impaired renal function, may be more likely to develop adverse effects.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient.

The frequency estimates in the following table were derived from controlled studies in hypertensive patients in which adverse reactions were either volunteered by the patient (US studies) or elicited, eg, by checklist (foreign studies). The reported frequency of elicited adverse effects was higher for both TENORMIN and placebo-treated patients than when these reactions were volunteered. Where frequency of adverse effects of TENORMIN and placebo is similar, causal relationship to TENORMIN is uncertain.

	Volunteered (US Studies)		Total - Volunteered and Elicited (Foreign + US Studies)	
	Atenolol (n = 164) %	Placebo (n = 206) %	Atenolol (n = 399) %	Placebo (n = 407) %
CARDIOVASCULAR				
Bradycardia	3	0	3	0
Cold Extremities	0	0.5	12	5
Postural Hypotension	2	1	4	5
Leg Pain	0	0.5	3	1
CENTRAL NERVOUS SYSTEM/ NEUROMUSCULAR				
Dizziness	4	1	13	6
Vertigo	2	0.5	2	0.2
Light-headedness	1	0	3	0.7
Tiredness	0.6	0.5	26	13
Fatigue	3	1	6	5
Lethargy	1	0	3	0.7
Drowsiness	0.6	0	2	0.5
Depression	0.6	0.5	12	9
Dreaming	0	0	3	1
GASTROINTESTINAL				
Diarrhea	2	0	3	2
Nausea	4	1	3	1
RESPIRATORY (see WARNINGS)				
Wheeziness	0	0	3	3
Dyspnea	0.6	1	6	4

Acute Myocardial Infarction: In a series of investigations in the treatment of acute myocardial infarction, bradycardia and hypotension occurred more commonly, as expected for any beta blocker, in atenolol-treated patients than in control patients. However, these usually responded to atropine and/or to withholding further dosage of atenolol. The incidence of heart failure was not increased by atenolol. Inotropic agents were infrequently used. The reported frequency of these and other events occurring during these investigations is given in the following table.

In a study of 477 patients, the following adverse events were reported during either intravenous and/or oral atenolol administration:

	Conventional Therapy Plus Atenolol (n=244)		Conventional Therapy Alone (n=233)	
Bradycardia	43	(18%)	24	(10%)
Hypotension	60	(25%)	34	(15%)
Bronchospasm	3	(1.2%)	2	(0.9%)
Heart Failure	46	(19%)	56	(24%)
Heart Block	11	(4.5%)	10	(4.3%)
BBB + Major Axis Deviation	16	(6.6%)	28	(12%)
Supraventricular Tachycardia	28	(11.5%)	45	(19%)
Atrial Fibrillation	12	(5%)	29	(11%)
Atrial Flutter	4	(1.6%)	7	(3%)
Ventricular Tachycardia	39	(16%)	52	(22%)
Cardiac Reinfarction	0	(0%)	6	(2.6%)
Total Cardiac Arrests	4	(1.6%)	16	(6.9%)
Nontatal Cardiac Arrests	4	(1.6%)	12	(5.1%)
Deaths	7	(2.9%)	16	(6.9%)
Cardiogenic Shock	1	(0.4%)	4	(1.7%)
Development of Ventricular Septal Defect	0	(0%)	2	(0.9%)
Development of Mitral Regurgitation	0	(0%)	2	(0.9%)
Renal Failure	1	(0.4%)	0	(0%)
Pulmonary Emboli	3	(1.2%)	0	(0%)

In the subsequent International Study of Infarct Survival (ISIS-1) including over 16,000 patients of whom 8,037 were randomized to receive TENORMIN treatment, the dosage of intravenous and subsequent oral TENORMIN was either discontinued or reduced for the following reasons:

	Reasons for Reduced Dosage IV Atenolol Reduced Dose (< 5mg)*		Oral Partial Dose	
Hypotension/Bradycardia	105	(1.3%)	1168	(14.5%)
Cardiogenic Shock	4	(.04%)	35	(.44%)
Reinfarction	0	(0%)	5	(.06%)
Cardiac Arrest	5	(.06%)	28	(.34%)
Heart Block (> first degree)	5	(.06%)	143	(1.7%)
Cardiac Failure	1	(.01%)	233	(2.9%)
Arrhythmias	3	(.04%)	22	(.27%)
Bronchospasm	1	(.01%)	50	(.62%)

*Full dosage was 10 mg and some patients received less than 10 mg but more than 5 mg.

During postmarketing experience with TENORMIN, the following have been reported in temporal relationship to the use of the drug: elevated liver enzymes and/or bilirubin, impotence, Peyronie's disease, psoriasiform rash, reversible alopecia, and thrombocytopenia. TENORMIN, like other beta blockers, has been associated with the development of antinuclear antibodies (ANA) and lupus syndrome.

POTENTIAL ADVERSE EFFECTS: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents, and may be considered potential adverse effects of TENORMIN.

Hematologic: Agranulocytosis, purpura.

Allergic: Fever, combined with aching and sore throat, laryngospasm, and respiratory distress.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation of time and place; short-term memory loss; emotional lability with slightly clouded sensorium; and, decreased performance on neuropsychometrics.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Other: Erythematous rash, Raynaud's phenomenon.

Miscellaneous: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small, and in most cases, the symptoms have cleared when treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Patients should be closely monitored following cessation of therapy. (SEE DOSAGE AND ADMINISTRATION.)

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with TENORMIN. Furthermore, a number of patients who had previously demonstrated established practolol reactions were transferred to TENORMIN therapy with subsequent resolution or quiescence of the reaction.

OVERDOSAGE: Overdosage with TENORMIN has been reported with patients surviving acute doses as high as 5 g. One death was reported in a man who may have taken as much as 10 g acutely.

The predominant symptoms reported following TENORMIN overdose are lethargy, disorder of respiratory drive, wheezing, sinus pause, and bradycardia. Additionally, common effects associated with overdosage of any beta-adrenergic blocking agent and which might also be expected in TENORMIN overdose are congestive heart failure, hypotension, bronchospasm, and/or hypoglycemia.

Treatment of overdose should be directed to the removal of any unabsorbed drug by induced emesis, gastric lavage, or administration of activated charcoal. TENORMIN can be removed from the general circulation by hemodialysis. Other treatment modalities should be employed at the physician's discretion and may include:

BRADYCARDIA: Atropine intravenously. If there is no response to vagal blockade, give isoproterenol cautiously. In refractory cases, a transvenous cardiac pacemaker may be indicated.

HEART BLOCK (SECOND OR THIRD DEGREE): Isoproterenol or transvenous cardiac pacemaker.

CARDIAC FAILURE: Digitalize the patient and administer a diuretic. Glucagon has been reported to be useful.

HYPOTENSION: Vasopressors such as dopamine or norepinephrine (levarterenol). Monitor blood pressure continuously.

BRONCHOSPASM: A beta$_2$ stimulant such as isoproterenol or terbutaline and/or aminophylline.

HYPOGLYCEMIA: Intravenous glucose.

Based on the severity of symptoms, management may require intensive support care and facilities for applying cardiac and respiratory support.

DOSAGE AND ADMINISTRATION: Hypertension: The initial dose of TENORMIN is 50 mg given as one tablet a day either alone or added to diuretic therapy. The full effect of this dose will usually be seen within one to two weeks. If an optimal response is not achieved, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Increasing the dosage beyond 100 mg a day is unlikely to produce any further benefit.

TENORMIN may be used alone or concomitantly with other antihypertensive agents including thiazide-type diuretics, hydralazine, prazosin, and alpha-methyldopa.

Angina Pectoris: The initial dose of TENORMIN is 50 mg given as one tablet a day. If an optimal response is not achieved within one week, the dosage should be increased to TENORMIN 100 mg given as one tablet a day. Some patients may require a dosage of 200 mg once a day for optimal effect.

Twenty-four hour control with once daily dosing is achieved by giving doses larger than necessary to achieve an immediate maximum effect. The maximum early effect on exercise tolerance occurs with doses of 50 to 100 mg, but at these doses the effect at 24 hours is attenuated, averaging about 50% to 75% of that observed with once a day oral doses of 200 mg.

Acute Myocardial Infarction: In patients with definite or suspected acute myocardial infarction, treatment with TENORMIN I.V. Injection should be initiated as soon as possible after the patient's arrival in the hospital and after eligibility is established. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized. Treatment should begin with the intravenous administration of 5 mg TENORMIN over 5 minutes followed by another 5 mg intravenous injection 10 minutes later. TENORMIN I.V. Injection should be administered under carefully controlled conditions including monitoring of blood pressure, heart rate, and electrocardiogram. Dilutions of TENORMIN I.V. Injection in Dextrose Injection USP, Sodium Chloride Injection USP, or Sodium Chloride and Dextrose Injection may be used. These admixtures are stable for 48 hours if they are not used immediately.

In patients who tolerate the full intravenous dose (10 mg), TENORMIN Tablets 50 mg should be initiated 10 minutes after the last intravenous dose followed by another 50 mg oral dose 12 hours later. Thereafter, TENORMIN can be given orally either 100 mg once daily or 50 mg twice a day for a further 6-9 days or until discharge from the hospital. If bradycardia or hypotension requiring treatment or any other untoward effects occur, TENORMIN should be discontinued.

Data from other beta blocker trials suggest that if there is any question concerning the use of IV beta blocker or clinical estimate that there is a contraindication, the IV beta blocker may be eliminated and patients fulfilling the safety criteria may be given TENORMIN Tablets 50 mg twice daily or 100 mg once a day for at least seven days (if the IV dosing is excluded).

Although the demonstration of efficacy of TENORMIN is based entirely on data from the first seven postinfarction days, data from other beta blocker trials suggest that treatment with beta blockers that are effective in the postinfarction setting may be continued for one to three years if there are no contraindications.

TENORMIN is an additional treatment to standard coronary care unit therapy.

Elderly Patients or Patients with Renal Impairment: TENORMIN is excreted by the kidneys; consequently dosage should be adjusted in cases of severe impairment of renal function. Some reduction in dosage may also be appropriate for the elderly, since decreased kidney function is a physiologic consequence of aging. Atenolol excretion would be expected to decrease with advancing age.

No significant accumulation of TENORMIN occurs until creatinine clearance falls below 35 mL/min/1.73m^2. Accumulation of atenolol and prolongation of its half-life were studied in subjects with creatinine clearance between 5 and 105 mL/min. Peak plasma levels were significantly increased in subjects with creatinine clearances below 30 mL/min.

The following maximum oral dosages are recommended for elderly renally-impaired patients and for patients with renal impairment due to other causes:

Creatinine Clearance (mL/min/1.73m^2)	Atenolol Elimination Half-Life (h)	Maximum Dosage
15-35	16-27	50 mg daily
<15	>27	25 mg daily

Some renally-impaired or elderly patients being treated for hypertension may require a lower starting dose of TENORMIN: 25 mg given as one tablet a day. If this 25 mg dose is used, assessment of efficacy must be made carefully. This should include measurement of blood pressure just prior to the next dose ("trough" blood pressure) to ensure that the treatment effect is present for a full 24 hours.

Although a similar dosage reduction may be considered for elderly and/or renally-impaired patients being treated for indications other than hypertension, data are not available for these patient populations.

Patients on hemodialysis should be given 25 mg or 50 mg after each dialysis; this should be done under hospital supervision as marked falls in blood pressure can occur.

Cessation of Therapy in Patients with Angina Pectoris: If withdrawal of TENORMIN therapy is planned, it should be achieved gradually and patients should be carefully observed and advised to limit physical activity to a minimum.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: TENORMIN Tablets: Tablets of 25 mg atenolol, NDC 0310-0107 (round, flat, uncoated white tablets with "T" debossed on one side and 107 debossed on the other side) are supplied in bottles of 100 tablets.

Tablets of 50 mg atenolol, NDC 0310-0105 (round, flat, uncoated white tablets identified with ICI debossed on one side and 105 debossed on the other side, bisected) are supplied in bottles of 100 tablets and 1000 tablets, and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Tablets of 100 mg atenolol, NDC 0310-0101 (round, flat, uncoated white tablets with ICI debossed on one side and 101 debossed on the other side) are supplied in bottles of 100 tablets and unit dose packages of 100 tablets. These tablets are distributed by ICI Pharma.

Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in well-closed, light resistant containers.

TENORMIN I.V. Injection: TENORMIN I.V. Injection, NDC 0310-0108, is supplied as 5 mg atenolol in 10 mL ampules of isotonic citrate-buffered aqueous solution.

Protect from light. Keep ampules in outer packaging until time of use. Store at room temperature.

REV W 11/91

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Wilmington, Delaware 19897 USA

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rectly identified accessory pathway locations in 18 of 19 patients at a regional level and was incorrect in 1. Technically adequate echocardiographic cine images were obtained in 17 of 19 patients. Echocardiographic phase imaging correctly identified accessory pathway location in all 17 patients at a regional level. In conclusion, administration of adenosine markedly accentuates preexcitation, allowing for more accurate electrocardiographic and echocardiographic (cine-loop and phase imaging) accessory pathway localization.

1186

Differences Between Predictive Characteristics of Signal-Averaged Electrocardiographic Variables for Postinfarction Sudden Death and Ventricular Tachycardia

Olusola Odemuyiwa, Marek Malik, Jan Poloniecki, Thomas Farrell, Teri Millane, Piotr Kulakowski, Anne Staunton, Alexander Matthies, and A. John Camm

The predictive values of the standard time-domain signal-averaged (SA) electrocardiographic variables for ventricular tachycardia and sudden death were compared in 332 postinfarction patients. During a follow-up period of ≥6 months, there were 12 sudden deaths (3.6%), 14 patients (4.2%) developed spontaneous sustained ventricular tachycardia, and 20 (6%) died of circulatory failure. Optimal criteria for predicting ventricular tachycardia required the positivity of ≥2 of the standard time-domain SA electrocardiographic variables, whereas optimal criteria for predicting sudden death required the positivity of all 3 variables. For a sensitivity of 70%, positive predictive accuracy was 31% for predicting sudden death, and 13% for predicting ventricular tachycardia. Differences between predictive characteristics of SA electrocardiographic variables may be used to refine postinfarction risk stratification.

1193

Variations in Expression and Treatment of Transient Neurocardiogenic Instability

Otto G. Thilenius, Karen J. Ryd, and Janet Husayni

This study describes the response of 104 pediatric patients with neurocardiogenic instability to head-up tilt stress. Five stages are identified, ranging from marked fluctuation in heart rate to full syncope. Unusual responses and individual variations in response to the tilt stress are reported. Eighty-four percent of the patients tested abnormal during the tilt study. Sixty-eight percent of these patients were given a β blocker, with excellent suppression in symptoms. Neurocardiogenic instability is a spectrum of symptoms and is apparently a common occurrence between age 10 and 20 years. It is not a "disease" but a transient phase of instability in control of heart rate and blood pressure.

SYSTEMIC HYPERTENSION

1196
Racial Differences in Left Ventricular Structure in Healthy Young Adults

Alan L. Hinderliter, Kathleen C. Light, and Park W. Willis IV

Racial differences in cardiac structure and function were studied in 62 black and 71 white healthy young adults. The 2 groups were similar in age, gender composition, and resting and daytime ambulatory blood pressures. Although there were no significant differences between black and white subjects in left ventricular (LV) mass index, relative wall thickness was significantly greater in blacks. This difference was found in both men and women. Black subjects also had a higher resting systemic vascular resistance index and lower resting cardiac index. LV fractional shortening and diastolic filling were similar in the 2 racial groups. These results suggest that racial differences in LV structure and systemic hemodynamics exist even in patients without sustained hypertension. In our study population, the greater relative wall thickness in black subjects was not accompanied by significant differences in LV systolic function or diastolic filling.

1200
Comparison of the Effects of Isradipine and Lisinopril on Left Ventricular Structure and Function in Essential Hypertension

Edith C. Bielen, Robert H. Fagard, Paul J. Lijnen, Tikma B. Tjandra-Maga, René Verbesselt, and Antoon K. Amery

In a 1-year study, 32 patients with essential hypertension were randomized to treatment with either the converting enzyme inhibitor lisinopril or the calcium antagonist isradipine to compare the effects on cardiac structure and function; hydrochlorothiazide could be added, if necessary. The decrease in left ventricular (LV) mass was related to the decrease in systolic blood pressure (BP) for the total study group and for each treatment group separately. During the subsequent 3-week run-out period on placebo, BP and LV mass increased again. It was concluded that during and after antihypertensive therapy, BP has a major role in the development and reversal of LV hypertrophy in essential hypertension. During active treatment, afterload decreased and LV systolic function improved; LV diastolic function improved without significant relation to the changes in LV mass or BP.

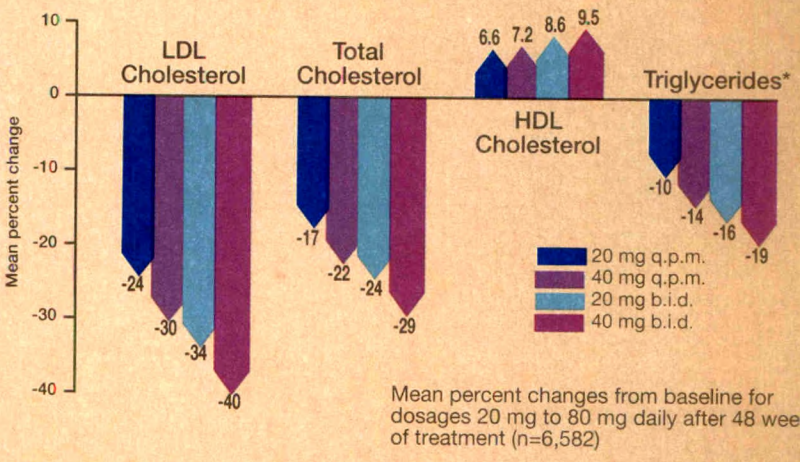
Continued on page A40

The largest U.S. double-blind, placebo-controlled trial of patients with moderate hypercholesterolemia

8,245 patients | **362 clinical sites** | **48 weeks**

EXPANDED CLINICAL EVALUATION OF LOVASTATIN
THE EXCEL STUDY

Excellent efficacy in lowering LDL and total cholesterol[1]



Mean percent changes from baseline for dosages 20 mg to 80 mg daily after 48 weeks of treatment (n=6,582)

* Triglyceride values are expressed as median changes.

1. Bradford, R.H. et al.: Expanded clinical evaluation of lovastatin (EXCEL) study results: I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8,245 patients with moderate hypercholesterolemia, Arch. Intern. Med. *151*:43-49, January 1991.

For many patients with primary hypercholesterolemia (Types IIa and IIb) when diet and other nondrug therapies are inadequate

MEVACOR®
(LOVASTATIN)

Tablets: 10 mg, 20 mg, 40 mg

Proven in research. Proven in practice.

MSD
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MEVACOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations; in pregnant or lactating patients; and in women of childbearing age, except when such patients are highly unlikely to conceive.

For complete details on MEVACOR, including cautionary information regarding myopathy, drug interactions, and liver enzyme monitoring, please refer to the Prescribing Information.

For a brief summary of Prescribing Information, please see the next page of this advertisement.

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MEVACOR® *
(LOVASTATIN)

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation.

Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR may cause fetal harm when administered to a pregnant woman. Therefore, lovastatin is contraindicated during pregnancy. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued, and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: *Liver Dysfunction:* Marked persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least 1 year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), the incidence of marked persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

It is recommended that liver function tests be performed during therapy with lovastatin. Serum transaminases, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks during the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and, in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations are persistent beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms, and interruption of treatment was not required.

Skeletal Muscle: **Rhabdomyolysis has been associated with lovastatin therapy alone, when combined with immunosuppressive therapy including cyclosporine in cardiac transplant patients, and when combined in non-transplant patients with either gemfibrozil or lipid-lowering doses (≥1g/day) of nicotinic acid. Some of the affected patients had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. Acute renal failure from rhabdomyolysis has been seen more commonly with the lovastatin-gemfibrozil combination and has also been reported in transplant patients receiving lovastatin plus cyclosporine.**

Rhabdomyolysis with or without renal impairment has been reported in seriously ill patients receiving erythromycin concomitantly with lovastatin. Therefore, patients receiving concomitant lovastatin and erythromycin should be carefully monitored.

Fulminant rhabdomyolysis has been seen as early as 3 weeks after initiation of combined therapy with gemfibrozil and lovastatin, but may be seen after several months. For these reasons, it is felt that, in most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefits of combined therapy with lovastatin and gemfibrozil do not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of lovastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with lovastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. The monitoring of lovastatin drug and metabolite levels may be considered in transplant patients who are treated with immunosuppressives and lovastatin.

Lovastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis, including: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures.

Myalgia has been associated with lovastatin therapy. Transient, mildly elevated CPK levels are commonly seen in lovastatin-treated patients. However, in early clinical trials, approximately 0.5% of patients developed a myopathy, i.e., myalgia or muscle weakness associated with markedly elevated CPK levels. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 5 patients (0.1%) taking lovastatin alone (1 at 40 mg q.p.m. and 4 at 40 mg b.i.d.) developed myopathy (muscle symptoms and CPK levels >10 times the upper limit of normal). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Lovastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.

Most of the patients who have developed myopathy (including rhabdomyolysis) while taking lovastatin were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or lipid-lowering doses of nicotinic acid. In clinical trials, about 30% of patients on concomitant immunosuppressive therapy including cyclosporine developed myopathy, the corresponding percentages for gemfibrozil and niacin were approximately 5% and 2%, respectively.

In 6 patients with cardiac transplants taking immunosuppressive therapy including cyclosporine concomitantly with lovastatin 20 mg/day, the average plasma level of active metabolites derived from lovastatin was elevated to approximately 4 times the expected levels. Because of an apparent relationship between increased plasma levels of active metabolites derived from lovastatin and myopathy, the daily dosage in patients taking immunosuppressants should not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION). Even at this dosage, the benefits and risks of using lovastatin in patients taking immunosuppressants should be carefully considered.

PRECAUTIONS: *General:* Before instituting therapy with MEVACOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in the full Prescribing Information).

Lovastatin may elevate CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See WARNINGS, *Skeletal Muscle.*

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin-treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than 2-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Because lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites, interactions of other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies lovastatin was used concomitantly with beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on an mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR® [Lovastatin].)

There was an increase in incidence of papilloma in the nonglandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose-response relationship for hepatocellular carcinogenicity in males at drug exposures 2 to 7 times that of human exposure at 80 mg/day (doses in rats were 5, 30, and 180 mg/kg/day).

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) the human exposure based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose). MEVACOR should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking MEVACOR, it should be discontinued, and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children with lovastatin is not recommended at this time.

ADVERSE REACTIONS: MEVACOR® (Lovastatin) is generally well tolerated; adverse reactions usually have been mild and transient. Less than 1% of patients were discontinued from controlled clinical studies of up to 14 weeks due to adverse experiences attributable to MEVACOR. About 3% of patients were discontinued from extensions of these studies due to adverse experiences attributable to MEVACOR; about half of these patients were discontinued due to increases in serum transaminases. The median duration of therapy in these extensions was 5.2 years.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences that were rated by the investigator as possibly, probably, or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Clinical Adverse Experiences: Adverse experiences reported in patients (%) treated with MEVACOR (n=613) in controlled clinical studies are: *Gastrointestinal:* constipation, 4.9; diarrhea, 5.5; dyspepsia, 3.9; flatus, 6.4; abdominal pain/cramps, 5.7; heartburn, 1.6; nausea, 4.7; *Musculoskeletal:* muscle cramps, 1.1; myalgia, 2.4; *Nervous System/Psychiatric:* dizziness, 2.0; headache, 9.3; *Skin:* rash/pruritus, 5.2; *Special Senses:* blurred vision, 1.5; dysgeusia, 0.8.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS).

About 11% of patients had elevations of creatine phosphokinase (CPK) levels of at least twice the normal value on one or more occasions. The corresponding values for the control agents were cholestyramine, 9%, and probucol, 2%. This was attributable to the noncardiac fraction of CPK. Large increases in CPK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Clinical Adverse Experiences: MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total cholesterol 240 to 300 mg/dL [6.2–7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably, or definitely drug related in ≥1% of any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

		MEVACOR			
	Placebo (n=1,663) %	20 mg q.p.m. (n=1,642) %	40 mg q.p.m. (n=1,645) %	20 mg b.i.d. (n=1,646) %	40 mg b.i.d. (n=1,649) %
Body as a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably, or definitely drug related in 0.5 to 1% of patients in any drug-treated group are listed below. In all these cases, the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL cholesterol than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with immunosuppressive drugs, gemfibrozil, or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: an apparent hypersensitivity syndrome has been reported rarely that has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE: After oral administration of MEVACOR to mice, the median lethal dose observed was >15 g/m².

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5 to 6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION: The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR. MEVACOR should be given with meals.

The recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 20 to 80 mg/day in single or divided doses; the maximum recommended dose is 80 mg/day. Adjustments of dosage should be made at intervals of 4 weeks or more. Doses should be individualized according to the patient's response (see Tables I to IV under CLINICAL PHARMACOLOGY, *Clinical Studies* in the full Prescribing Information for dose-response results).

In patients taking immunosuppressive drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

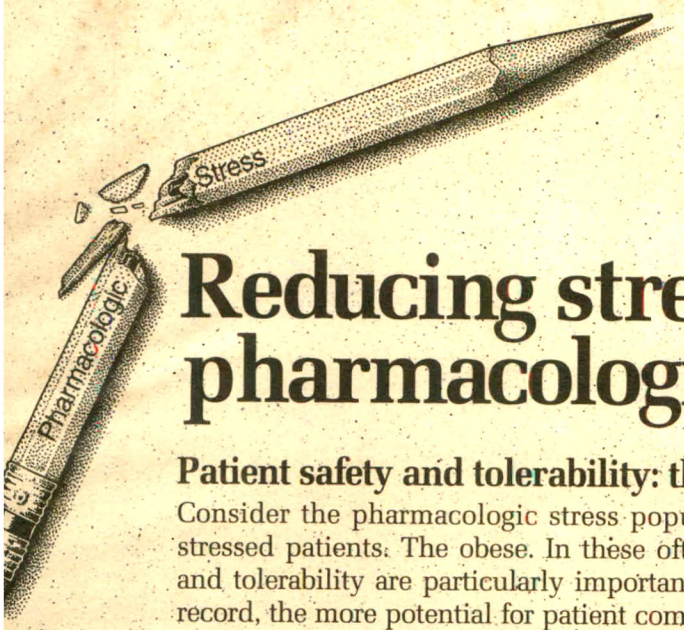
Cholesterol levels should be monitored periodically, and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall below the targeted range.

Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY in the full Prescribing Information and WARNINGS, *Skeletal Muscle*).

For more detailed information, consult your MSD Representative or see the Prescribing Information.

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Reducing stress in pharmacologic stress testing

Patient safety and tolerability: the stress factors

Consider the pharmacologic stress population. Old patients. Frail patients. Submaximally stressed patients. The obese. In these often vulnerable or compromised patient types, safety and tolerability are particularly important. The more certain an agent's safety and tolerability record, the more potential for patient comfort and physician confidence. Use of an agent with a proven tolerability and safety record can reduce the overall stress to the patient, while easing the emotional stress to the physician.

A safety record that spans more than a decade

I.V. Persantine® (dipyridamole USP) has a safety profile established in over a decade of clinical testing.[1,2*] And, based on information from over 250,000 patient studies, I.V. Persantine is generally well tolerated.[†] Such an established record in pharmacologic stress creates a standard by which to compare other agents.

Generally well-tolerated stress begins with smooth, gradual onset of effect

Pharmacologic stress with I.V. Persantine takes effect smoothly with a 4-minute infusion, followed within 5 minutes with the appropriate thallium dose. This allows the patient to become accustomed to the "stressing" process more gradually: there is no "sudden impact." Additionally, the time is short enough to allow an expedient, relatively uncomplicated imaging procedure.

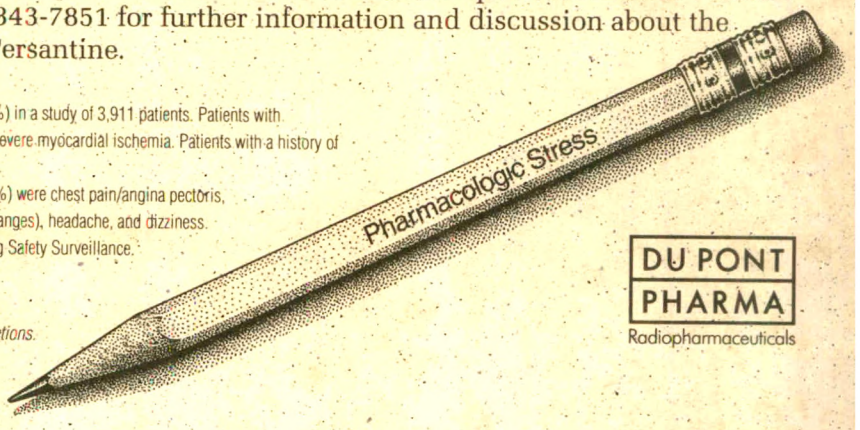
Convenient, easy-to-follow protocol minimizes procedural frustrations

The procedural logistics of pharmacologic stress can be another source of emotional stress to the physician or staff. With I.V. Persantine, there's a flexible, easy-to-follow protocol. No infusion pump needed. No need for site-specific injection. And no extra I.V. line for the imaging agent.

When you stress more assured, you can rest more assured

Based on its proven safety profile and generally well-tolerated effect, I.V. Persantine sets a solid foundation to help reduce the stress that can sometimes be associated with pharmacologic stress.

Stress the facts in pharmacologic stress...call the Du Pont Radiopharmaceuticals Nuclear Cardiology Hotline at 1-800-343-7851 for further information and discussion about the proven safety profile of I.V. Persantine.



*Severe adverse events have occurred infrequently (<0.3%) in a study of 3,911 patients. Patients with a history of unstable angina may be at a greater risk for severe myocardial ischemia. Patients with a history of asthma may be at a greater risk for bronchospasm.
In the same study, the most frequent adverse events (>2%) were chest pain/angina pectoris, electrocardiographic changes (most commonly, ST-T changes), headache, and dizziness.

†Du Pont Merck Pharmaceutical Company Post-Marketing Safety Surveillance.

Please see brief summary of prescribing information on reverse for contraindications, warnings, and adverse reactions.

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Radiopharmaceuticals

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I.V. PERSANTINE®

(dipyridamole USP) Injection 5mg/ml

References: 1. Ranhosky A, Kemptherne-Rawson J, et al. *Circulation.* 1990;81:1205-1209. **2.** Data on file, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn.

I.V. PERSANTINE®

(dipyridamole USP) Injection 5mg/ml

Brief Summary of Prescribing Information

CONTRAINDICATIONS Hypersensitivity to dipyridamole.

WARNINGS Serious adverse reactions associated with the administration of intravenous Persantine® (dipyridamole USP) have included fatal and non-fatal myocardial infarction, ventricular fibrillation, symptomatic ventricular tachycardia, transient cerebral ischemia, and bronchospasm.

In a study of 3911 patients given intravenous Persantine as an adjunct to thallium myocardial perfusion imaging, two types of serious adverse events were reported: 1) four cases of myocardial infarction (0.1%), two fatal (0.05%), and two non-fatal (0.05%); and 2) six cases of severe bronchospasm (0.2%). Although the incidence of these serious adverse events was small (0.3%, 10 of 3911), the potential clinical information to be gained through use of intravenous Persantine thallium imaging must be weighed against the risk to the patient. Patients with a history of unstable angina may be at a greater risk for severe myocardial ischemia. Patients with a history of asthma may be at a greater risk for bronchospasm during IV Persantine use.

When thallium myocardial perfusion imaging is performed with intravenous Persantine, parenteral aminophylline should be readily available for relieving adverse events such as bronchospasm or chest pain. Vital signs should be monitored during, and for 10-15 minutes following, the intravenous infusion of Persantine and an electrocardiographic tracing should be obtained using at least one chest lead. Should severe chest pain or bronchospasm occur, parenteral aminophylline may be administered by slow intravenous injection (50-100 mg over 30-60 seconds) in doses ranging from 50 to 250 mg. In the case of severe hypotension, the patient should be placed in a supine position with the head tilted down if necessary, before administration of parenteral aminophylline. If 250 mg of aminophylline does not relieve chest pain symptoms within a few minutes, sublingual nitroglycerin may be administered. If chest pain continues despite use of aminophylline and nitroglycerin, the possibility of myocardial infarction should be considered. If the clinical condition of a patient with an adverse event permits a one minute delay in the administration of parenteral aminophylline, thallium-201 may be injected and allowed to circulate for one minute before the injection of aminophylline. This will allow initial thallium perfusion imaging to be performed before reversal of the pharmacologic effects of Persantine on the coronary circulation.

PRECAUTIONS See WARNINGS.

Drug Interactions Oral maintenance theophylline may abolish the coronary vasodilatation induced by intravenous Persantine® (dipyridamole USP) administration. This could lead to a false negative thallium imaging result.

Carcinogenesis, Mutagenesis, Impairment of Fertility In studies in which dipyridamole was administered in the feed at doses of up to 75 mg/kg/day (9.4 times* the maximum recommended daily human oral dose) in mice (up to 128 weeks in males and up to 142 weeks in females) and rats (up to 111 weeks in males and females), there was no evidence of drug related carcinogenesis. Mutagenicity tests of dipyridamole with bacterial and mammalian cell systems were negative. There was no evidence of impaired fertility when dipyridamole was administered to male and female rats at oral doses up to 500 mg/kg/day (63 times* the maximum recommended daily human oral dose). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was, however, observed at 1250 mg/kg/day.

*Calculation based on assumed body weight of 50 kg.

Pregnancy Category B Reproduction studies performed in mice and rats at daily oral doses of up to 125 mg/kg (15.6 times* the maximum recommended daily human oral dose) and in rabbits at daily oral doses of up to 20 mg/kg (2.5 times* the maximum recommended daily human oral dose) have revealed no evidence of impaired embryonic development due to dipyridamole. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed.

*Calculation based on assumed body weight of 50 kg.

Nursing Mothers Dipyridamole is excreted in human milk.

Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS Adverse reaction information concerning intravenous Persantine® (dipyridamole USP) is derived from a study of 3911 patients in which intravenous Persantine was used as an adjunct to thallium myocardial perfusion imaging and from spontaneous reports of adverse reactions and the published literature.

Serious adverse events (fatal and non-fatal myocardial infarction, severe ventricular arrhythmias, and serious CNS abnormalities) are described previously (see WARNINGS).

In the study of 3911 patients, the most frequent adverse reactions were: chest pain/angina pectoris (19.7%), electrocardiographic changes (most commonly ST-T changes) (15.9%), headache (12.2%), and dizziness (11.8%).

Adverse reactions occurring in greater than 1% of the patients in the study are shown in the following table:

	Incidence (%) of Drug-Related Adverse Events
Chest Pain/Angina Pectoris	19.7
Headache	12.2
Dizziness	11.8
Electrocardiographic Abnormalities/ST-T changes	7.5
Electrocardiographic Abnormalities/Extrasystoles	5.2
Hypotension	4.6
Nausea	4.6
Flushing	3.4
Electrocardiographic Abnormalities/Tachycardia	3.2
Dyspnea	2.6
Pain Unspecified	2.6
Blood Pressure Lability	1.6
Hypertension	1.5
Paresthesia	1.3
Fatigue	1.2

Less common adverse reactions occurring in 1% or less of the patients within the study included:

Cardiovascular System: Electrocardiographic abnormalities unspecified (0.8%), arrhythmia unspecified (0.6%), palpitation (0.3%), ventricular tachycardia (0.2% see WARNINGS), bradycardia (0.2%), myocardial infarction (0.1% see WARNINGS), AV block (0.1%), syncope (0.1%), orthostatic hypotension (0.1%), atrial fibrillation (0.1%), supraventricular tachycardia (0.1%), ventricular arrhythmia unspecified (0.03% see WARNINGS), heart block unspecified (0.03%), cardiomyopathy (0.03%), edema (0.03%).

Central and Peripheral Nervous System: Hypothesia (0.5%), hypertonia (0.3%), nervousness/anxiety (0.2%), tremor (0.1%), abnormal coordination (0.03%), somnolence (0.03%), dysphonia (0.03%), migraine (0.03%), vertigo (0.03%).

Gastrointestinal System: Dyspepsia (1.0%), dry mouth (0.8%), abdominal pain (0.7%), flatulence (0.6%), vomiting (0.4%), eructation (0.1%), dysphagia (0.03%), tenesmus (0.03%), appetite increased (0.03%).

Respiratory System: Pharyngitis (0.3%), bronchospasm (0.2% see WARNINGS), hyperventilation (0.1%), rhinitis (0.1%), coughing (0.03%), pleural pain (0.03%).

Other: Myalgia (0.9%), back pain (0.6%), injection site reaction unspecified (0.4%), diaphoresis (0.4%), asthenia (0.3%), malaise (0.3%), arthralgia (0.3%), injection site pain (0.1%), rigor (0.1%) earache (0.1%), tinnitus (0.1%), vision abnormalities unspecified (0.1%), dysgeusia (0.1%), thirst (0.03%), depersonalization (0.03%), eye pain (0.03%), renal pain (0.03%), perineal pain (0.03%), breast pain (0.03%), intermittent claudication (0.03%), leg cramping (0.03%).

OVERDOSAGE No cases of overdosage in humans have been reported. It is unlikely that overdosage will occur because of the nature of use (i.e., single intravenous administration in controlled settings). See WARNINGS.

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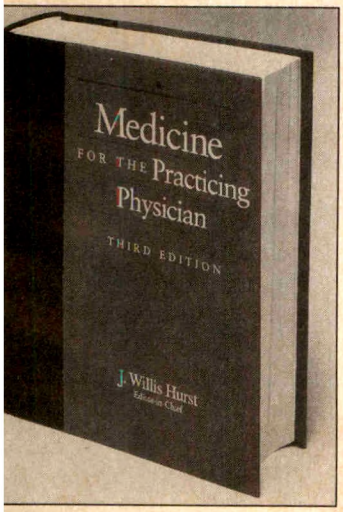
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CONGESTIVE HEART FAILURE

1207
Characteristics of Peak Aerobic Capacity in Symptomatic and Asymptomatic Subjects with Left Ventricular Dysfunction

Chang-seng Liang, Douglas K. Stewart, Thierry H. LeJemtel, Philip C. Kirlin, Kevin M. McIntyre, H. Thomas Robertson, Robert Brown, Andrea W. Moore, Karen L. Wellington, Linda Cahill, Marie Galvao, Patricia A. Woods, Carlos Garces, and Peter Held, for the Studies of Left Ventricular Dysfunction (SOLVD) Investigators

Peak aerobic performance was determined by expired gas analysis in subjects with depressed left ventricular (LV) ejection fraction (≤0.35) and a wide range of clinical manifestations of congestive heart failure (CHF) in the Studies of Left Ventricular Dysfunction. Subjects were divided into those with overt CHF needing treatment (treatment trial) and those who had neither overt CHF nor treatment for CHF (prevention trial). Treatment trial subjects exercised for a shorter time and attained a lower peak exercise oxygen consumption ($\dot{V}O_2$) and $\dot{V}O_2$ at anaerobic threshold than did prevention trial ones. Analysis of covariance showed that the differences in peak $\dot{V}O_2$ and $\dot{V}O_2$ at anaerobic threshold were statistically significant between the 2 trials after adjusting for age, gender, LV ejection fraction and New York Heart Association functional class. Thus, of subjects with reduced LV ejection fraction, those with no or minimal CHF have higher aerobic exercise performance than do those with overt CHF. This difference cannot be explained by gender, age, LV ejection fraction or New York Heart Association functional class.

1212
Long-Term Outcome in Patients with Congestive Heart Failure and Intact Systolic Left Ventricular Performance

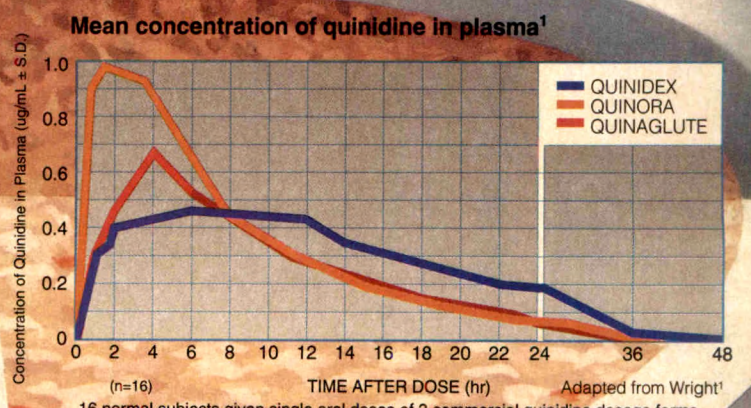
John F. Setaro, Robert Soufer, Michael S. Remetz, Robin A. Perlmutter, and Barry L. Zaret

To evaluate the long-term outcome in patients with clinical congestive heart failure (CHF) and preserved left ventricular (LV) systolic function (ejection fraction ≥45%), 7-year follow-up was obtained in 52 patients originally identified in 1982. Principal cardiovascular diagnoses included coronary artery disease in 27 (52%), hypertensive heart disease in 16 (31%), and restrictive cardiomyopathy in 7 (13%). Cardiovascular mortality was 46% (24 of 52), nonfatal cardiovascular morbidity 29% (15 of 52), and combined cardiovascular mortality and morbidity 75% (39 of 52), suggesting an unfavorable long-term prognosis for patients with CHF despite intact LV systolic performance.

Continued on page A43

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See brief summary of prescribing information on adjacent page.

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The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncracy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

References

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3. IMS National Prescription Audit, May 1991.

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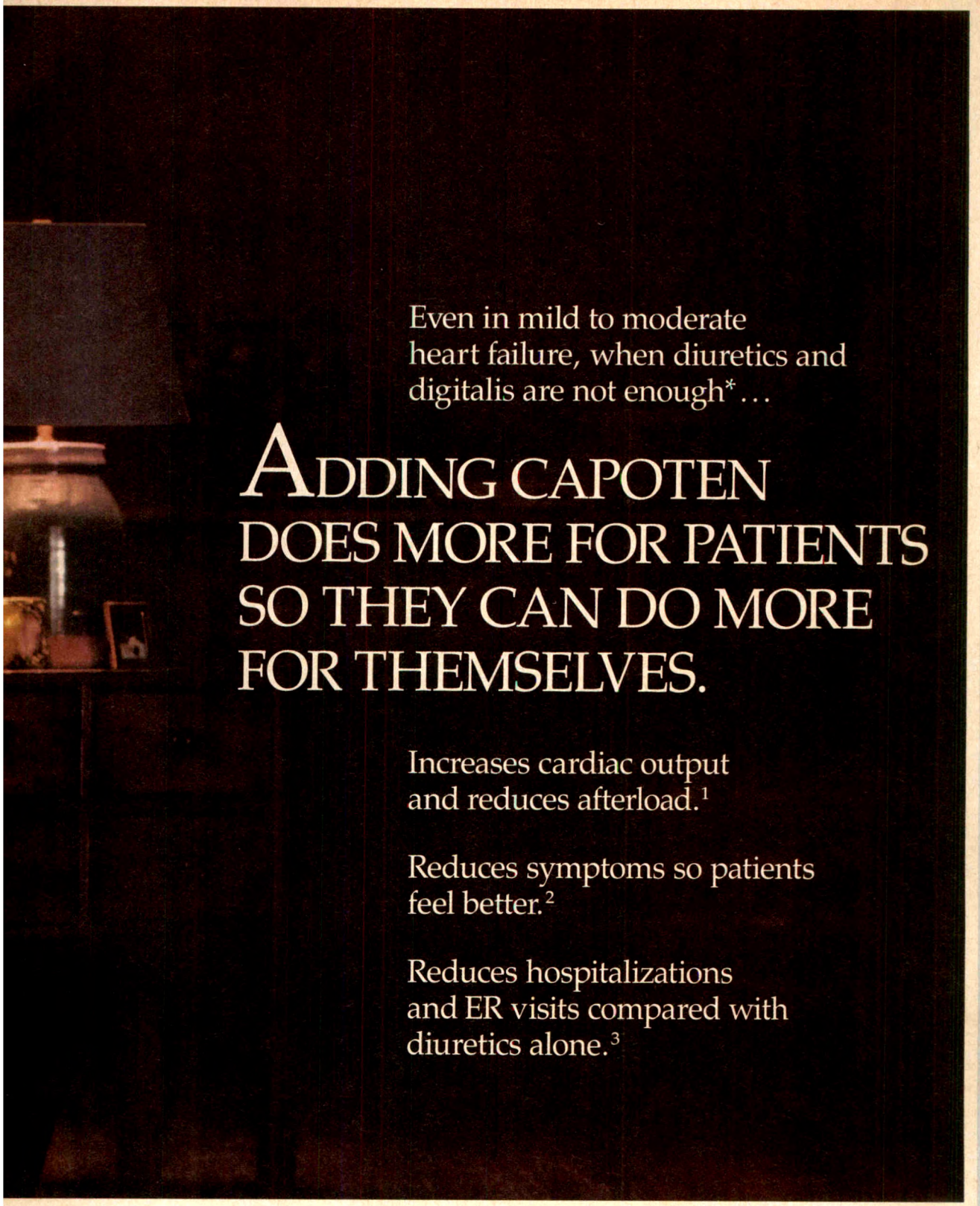
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USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS: Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia / Agranulocytosis: Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine $\geq$ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count $<1000/mm^3$) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS: Drug Interactions.) In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

Fetal / Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension–Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. (See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings.) *Hyperkalemia:* Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.) *Cough*—Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *Hypotension–Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Lithium—Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use: Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension with captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials (see PRECAUTIONS: General: *Cough*).

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Altered Laboratory Findings: *Serum Electrolytes:* Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of long-standing or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of: 12.5 mg in bottles of 100 and 1000; 25 mg in bottles of 100 and 1000; 50 mg in bottles of 100 and 1000; 100 mg of bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658Z)

References: 1. Physicians' Desk Reference®, 45th ed, Oradell, NJ. Medical Economics Co Inc, 1991 pp 2141-2143. 2. Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *JACC* 2:755-763, 1983. 3. The Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539-544, 1988.

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BRIEF SUMMARY

INDICATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of hypertension, alone or in combination with other antihypertensive drugs, and for the treatment of salt and fluid retention associated with congestive heart failure.
Usage in Pregnancy: See PRECAUTIONS.

CONTRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-derived drugs.

WARNINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, have been reported with the use of recommended doses of indapamide primarily in elderly females. Symptoms were reversed by electrolyte replenishment (see PRECAUTIONS). Hypokalemia occurs commonly with diuretics (see ADVERSE REACTIONS, hypokalemia), and electrolyte monitoring is essential. In general, diuretics should not be given with lithium.

PRECAUTIONS: Perform serum electrolyte determinations at appropriate intervals, especially in patients who are vomiting excessively or receiving parenteral fluids, in patients subject to electrolyte imbalance, or in patients on a salt-restricted diet. In addition, patients should be observed for clinical signs of fluid or electrolyte imbalance, such as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of hypokalemia secondary to diuresis and natriuresis is increased with larger doses, with brisk diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or ACTH. Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis, such as increased ventricular irritability.
Dilutional hyponatremia may occur in edematous patients; appropriate treatment is usually water restriction. In actual salt depletion, appropriate replacement is the treatment of choice. Chloride deficit is usually mild, not requiring specific treatment except in extraordinary circumstances (liver, renal disease).
Hyperuricemia may occur, and frank gout may be precipitated in certain patients receiving indapamide. Serum concentrations of uric acid should be monitored periodically.
Use with caution in patients with severe renal disease; consider withholding or discontinuing if progressive renal impairment is observed. Renal function tests should be performed periodically.
Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

DRUG INTERACTIONS: LOZOL may add to or potentiate the action of other antihypertensive drugs. The antihypertensive effect of the drug may be enhanced in the postsympathectomized patient. Indapamide may decrease arterial responsiveness to norepinephrine, but this does not preclude the use of norepinephrine.
In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with $\geq 5\%$ cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; $< 5\%$ cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Clinical hypokalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study (157 patients) potassium supplementation was given to 12% to 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
Keep tightly closed. Store at room temperature. Avoid excessive heat.
Dispense in tight containers as defined in USP.
See product circular for full prescribing information. Revised: June 1990

References: 1. IMS National Prescription Audit (NPA), August 1991. Compared with year-to-date August 1991 percentage growth in new prescriptions among the 10 leading brands of diuretics. **2.** Scott-Levin Physician Drug and Diagnosis Audit (PDDA), July 1990–June 1991.

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CORONARY ARTERY DISEASE

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Importance of a Patent Infarct-Related Artery for Hospital and Late Survival After Direct Coronary Angioplasty for Acute Myocardial Infarction

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The importance of a patent infarct-related artery (IRA) for hospital and late survival was examined in 383 patients with acute myocardial infarction treated with direct coronary angioplasty. At hospital discharge, 317 of 348 patients (91%) had a patent IRA and mean follow-up left ventricular (LV) ejection fraction (EF) was 58%. Cardiac survival after hospital discharge at 1, 3 and 6 years was 99, 95 and 90%. Patency of the IRA was the most important determinant of hospital mortality: patent versus occluded IRA, 5 vs 39% mortality, p <0.001. Follow-up LVEF was the most important determinant of late cardiac mortality: follow-up LVEF ≥45 versus <45%, 2 versus 24% mortality, p <0.001. Patency of the IRA was not a significant predictor of late cardiac mortality in the group as a whole: patent versus occluded IRA, 4.7 versus 6.5% mortality, p = 0.67. In the subgroup of patients with depressed initial LVEF <45%, patency was a significant predictor of late cardiac mortality: patent versus occluded IRA, 9.2 versus 40% mortality, p = 0.03. Patients with a patent IRA had better recovery of LV function than patients with an occluded IRA (follow-up LVEF 58.5 versus 47.6%, p <0.001). When late cardiac mortality was adjusted for differences in follow-up LVEF, patency was no longer a significant predictor of late mortality.

Our results indicate patency of the IRA is the most important determinant of hospital survival, and LV function (measured after recovery) is the most important determinant of late cardiac survival. Patency of the IRA is important for preservation of LV function, but is not an independent determinant of late cardiac survival.

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Myocardial reperfusion has been shown to improve both short- and long-term survival in acute myocardial infarction (AMI).[1,2] Although this has been thought to be due primarily to the effects of reperfusion on preservation of left ventricular (LV) function, several observations suggest other factors may be important.[3,4] The Western Washington trial found improved late survival in patients who had successful reperfusion, despite the fact that there was no improvement in LV function.[5] The International Study of Infarct Survival-II trial showed improved survival in patients treated late at 6 to 24 hours after the onset of chest pain, at which time little or no salvage of myocardium would be expected.[2] These observations suggest that an open infarct vessel may be beneficial in improving survival, independent of its effect on preservation of LV function.[3,4] The purpose of this study was to evaluate the importance of a patent infarct-related artery (IRA) for hospital and late survival after direct coronary angioplasty for AMI.

METHODS

Study population: Our study population was selected from 636 patients with AMI who presented to our cardiology group from 1984 to 1988. Of these, 383 (60%) with electrocardiographic ST-segment elevation were treated with direct angioplasty, without prior thrombolytic therapy, and comprise our study group. The details of the selection criteria have previously been described.[6]

Treatment protocol: Patients were transported promptly from the emergency department to the cardiac catheterization laboratory where coronary intervention could generally be started within 30 to 60 minutes. Coronary reperfusion was established mechanically with the use of direct coronary angioplasty. Intravenous heparin was continued for 4 to 5 days after intervention keeping the partial thromboplastin time 2 to 3 times control. The details of the in-hospital treatment protocol have been described earlier.[6,7]

Follow-up angiography: Follow-up angiography was performed routinely during the first 3 years of the study, and when clinically indicated during the last 2 years of the study. LV ejection fraction (EF) was calculated from tracing contours of right anterior oblique ventriculograms using the area-length method with cor-

TABLE I Baseline Demographic, Clinical and Angiographic Characteristics of 383 Patients Treated with Direct Angioplasty

Characteristic	No. (%)
Age (years ± SD)	59 ± 11
Age ≥75 years	30 (7.8)
Men/women	277/106
Prior AMI	85 (22.0)
Prior coronary bypass surgery	12 (3.1)
Cardiogenic shock*	22 (5.7)
Anterior wall AMI	172 (45.0)
Reperfusion time (hours ± SD)	4.1 ± 3.2
Late reperfusion (>6 hours)	48 (12.5)
Multivessel coronary disease†	204 (53.0)
Initial LVEF (% ± SD)‡	52 ± 14
Initial LVEF <45%	97 (25.0)

*Blood pressure <85 mm Hg at presentation not responsive to intravenous fluids and associated with severe left ventricular dysfunction.
†>70% stenosis in 2 or 3 major epicardial coronary arteries.
‡n = 329. Left ventriculograms were not performed or were inadequate in 54 patients.
AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction.

rection for the 30° right anterior oblique projection.[8] Ventriculograms were excluded if there was frequent ectopy or inadequate opacification. Follow-up angiography was performed in 219 patients or 63% of hospital survivors at a mean follow-up time of 8 months. Left ventriculograms were adequate for measurement of follow-up LVEF in 196 patients or 56% of hospital survivors.

Patient follow-up: Follow-up information on patient status was obtained by hospital and office chart review and by telephone contact. The events recorded included death, cause of death, nonfatal reinfarction, coronary bypass surgery and repeat coronary angioplasty. Follow-up ranged from 1 to 6 years (mean 3.3). One patient was lost to follow-up in the first year and a total of 11 patients (3.2%) were lost to follow-up during the entire follow-up period.

Data analysis: Demographic, clinical and angiographic variables tested as predictors of hospital mortality included age, sex, prior myocardial infarction, prior coronary bypass surgery, cardiogenic shock, IRA, initial patency of the IRA, presence of multivessel disease, initial LVEF, and IRA patency immediately after the direct angioplasty procedure. The variables evaluated as predictors of late mortality include the aforementioned variables plus patency of the IRA at hospital discharge and LVEF measured at follow-up angiography. The IRA was classified as occluded at hospital discharge if the initial direct angioplasty procedure was unsuccessful or if there was reinfarction or angiographic documentation of reocclusion. Patients who had undergone coronary bypass surgery and those with reinfarction who achieved successful redilation were classified as having a patent IRA. Of the 317 patients classified as having a patent IRA at hospital discharge, all had angiographic documentation of acute patency and 216 patients had either angiographic documentation of late patency (192 patients) or had undergone coronary bypass surgery (24 patients). In 4 patients who died after hospital discharge without follow-up angiography, follow-up LVEF measured by radionuclide ventriculography was used in the analysis.

The chi-square statistic with Yates's correction for continuity was used as a test of the homogeneity of proportions in the univariate analysis of hospital and late mortality and dichotomous independent variables. Fisher's 2-tailed exact probabilities were calculated for all fourfold tables when 1 or more of the expected cell frequencies was <5. Student's *t* test for independent samples was used to analyze the difference in means of continuous variables. Kaplan-Meier survival curves were computed to examine differences in late survival potentially due to categorical demographic, clinical and angiographic variables.[9] Statistical significance of subgroup comparisons was determined by the Lee-Desu statistic. Logistic regression was used to evaluate the effects of categorical variables on hospital and late mortality when used in the multivariate predictive models. An attempt was also made to analyze the effects of categorical variables on late survival using a multivariate Cox proportional hazards model. Although there were too few deaths to test the assumptions of the proportional hazards model, the results presented are consistent with findings from the survival analyses using single independent variables. All analyses were performed with the SAS and SPSS-X statistical software.

RESULTS

Baseline characteristics: The baseline characteristics of the 383 patients treated with direct angioplasty are listed in Table I. Our study population included patients generally considered ineligible for thrombolytic therapy and known to be at increased risk of mortality, such as patients with cardiogenic shock (22 patients), prior coronary bypass surgery (12 patients), late presentation (48 patients), and elderly patients (30 patients).

Hospital outcome: Coronary angioplasty was performed successfully in 347 of 383 patients (91%), resulting in a patent IRA and <50% residual luminal stenosis. There were 35 hospital deaths (9.1%) and 23 patients (6.0%) had in-hospital nonfatal reinfarction. Coronary artery bypass surgery was performed in 26 patients (6.8%) and additional coronary angioplasty procedures were performed in 28 patients (7.3%) including 14 patients with emergency angioplasty for in-hospital reinfarction.

Predictors of hospital mortality: The predictors of hospital mortality from univariate and multivariate analyses are listed in Table II. The strongest independent predictor of hospital mortality was an occluded IRA (unsuccessful coronary angioplasty). There were 14 hospital deaths (39%) among 36 patients with an occluded IRA compared with 21 hospital deaths (5.1%) among 347 patients with a patent IRA ($p < 0.001$). Age and late reperfusion were also significant independent predictors of hospital mortality. Multivessel coronary disease and a depressed initial LVEF <45% approached significance as independent predictors of hospital mortality. Cardiogenic shock was not an independent predictor of mortality in this analysis because 6 patients (including 5 who died) were excluded owing to lack of initial LVEF data. When LVEF was not included in the multivariate analysis, cardiogenic shock was a strong independent predictor of hospital mortality.

TABLE II Univariate and Multivariate Predictors of Hospital Mortality After Direct PTCA for Acute Myocardial Infarction

Variable	No. of Pts. (n = 383)	No. (%) Died (n = 35)	Univariate p Value*	Multivariate Odds Ratio	95% CI
Occluded IRA	36	14 (38.9)	<0.001	3.22	1.68–6.17
Age ≥65 years	128	22 (17.2)	<0.001	1.93	1.15–3.22
Late reperfusion†	48	8 (16.7)	0.05	1.78	1.00–3.17
Multivessel CAD	204	29 (14.2)	<0.001	1.80	0.97–3.31
Initial LVEF <45%	97	16 (16.5)	<0.001	1.63	0.92–2.90
Cardiogenic shock	22	11 (50.0)	<0.001	1.57	0.76–3.24
Women	106	13 (12.3)	<0.001	1.41	0.83–2.42
Anterior wall AMI	172	21 (12.2)	0.06	1.35	0.76–2.41
Prior AMI	85	14 (16.5)	<0.01	1.30	0.73–2.31
Prior CABG	12	3 (25.0)	0.05	1.34	0.34–5.29

*Compares mortality of patients with variable present to mortality with variable absent.
†>6 hours.
AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CI = confidence interval; IRA = infarct-related artery; LVEF = left ventricular ejection fraction; PTCA = percutaneous transluminal coronary angioplasty.

TABLE III Univariate and Multivariate Predictors of Late Cardiac Mortality in Hospital Survivors After Direct PTCA for Acute Myocardial Infarction

Variable	No. of Pts. (n = 348)	No. (%) Died (n = 17)	Univariate p Value*	Multivariate Odds Ratio†	95% CI
Follow-up LVEF <45%	33	8 (24.2)	0.001	2.99	1.24–7.20
Initial LVEF <45%	81	9 (11.1)	0.01	1.72	0.62–4.79
Men	255	15 (5.9)	NS	2.64	0.77–9.08
Age ≥65 years	106	6 (5.7)	NS	1.95	0.87–4.33
Occluded IRA	31	2 (6.5)	NS	1.61	0.56–4.63
Anterior wall AMI	151	10 (6.6)	NS	1.39	0.56–3.42
Multivessel CAD	175	11 (6.3)	NS	1.34	0.58–3.09
Prior AMI	71	6 (8.5)	NS	1.07	0.48–2.35
Prior CABG	9	1 (11.1)	NS	1.05	0.25–4.37
Late reperfusion‡	40	0 (0)	NS	—	—
Cardiogenic shock	11	0 (0)	NS	—	—

*Compares mortality of patients with variable present to mortality with variable absent.
†This model includes only patients with both initial and follow-up LVEF data (n = 188).
‡>6 hours.
NS = not significant; other abbreviations as in Table II.

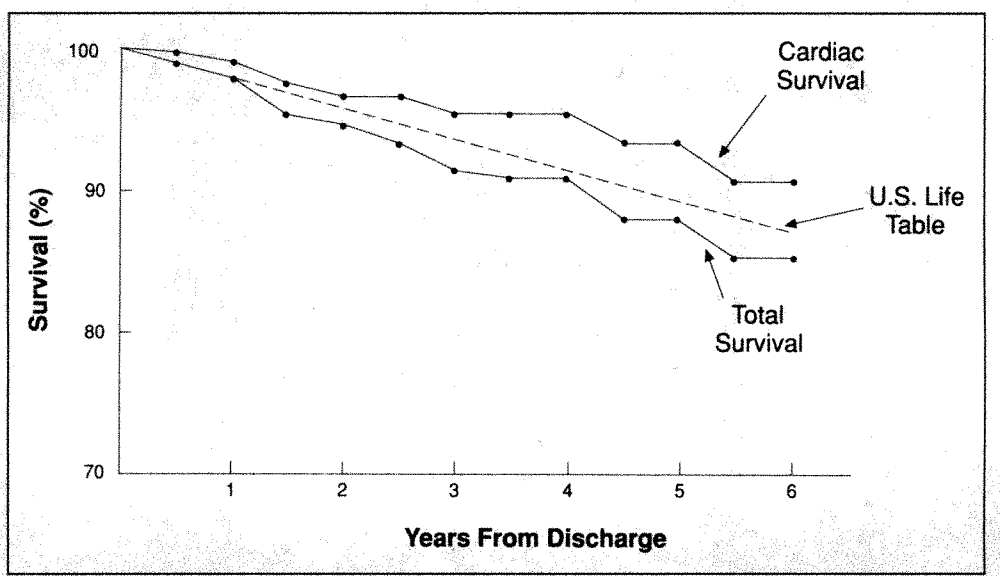


FIGURE 1. Kaplan-Meier survival curves for 348 patients discharged from the hospital after direct angioplasty for acute myocardial infarction. *Top curve*, cardiac survival; *bottom curve*, total survival; *middle curve*, survival curve for the United States population matched to our patients for age and sex.

Outcome after the hospital: Of the 383 patients treated with direct angioplasty, 348 were discharged from the hospital and followed for 1 to 6 years (mean 3.3). There were 31 late deaths, 17 cardiac and 14 noncardiac. The mechanism of cardiac death was sudden in 12, reinfarction in 1, congestive heart failure in 2, after coronary bypass surgery in 1, and uncertain in 1. The mean follow-up LVEF in 196 hospital survivors with follow-up left ventriculography was 58%. Coronary artery bypass surgery was performed in 23 patients (6.6%) after hospital discharge and additional coronary angioplasty procedures were performed in 54 patients (15.5%) including emergency angioplasty in 17 of 34 patients with late reinfarctions. Kaplan-Meier survival curves for total survival and cardiac survival are shown in Figure 1. The cardiac survival at 1 and 6 years was 99 and 90%, respectively.

Predictors of late cardiac mortality: The predictors of late cardiac mortality are listed in Table III. A depressed initial and follow-up LVEF were the only significant univariate predictors of late cardiac mortality. Late mortality in patients with an initial LVEF <45 versus ≥45% was 11.1 (9 of 81) versus 3.1% (7 of 224) ($p < 0.01$). The late mortality in patients with follow-up LVEF <45 versus ≥45% was 24.2 (8 of 33) versus 2.5% (4 of 163) ($p < 0.001$). A depressed follow-up LVEF was the only significant independent predictor of late cardiac mortality by multivariate analysis. Survival curves for patients with depressed versus preserved initial and follow-up LVEF are shown in Figures 2 and 3. Multivariate analysis of survival curves with the Cox proportional hazards model also showed that follow-up LVEF was the only significant independent predictor of late cardiac mortality. The importance of follow-up

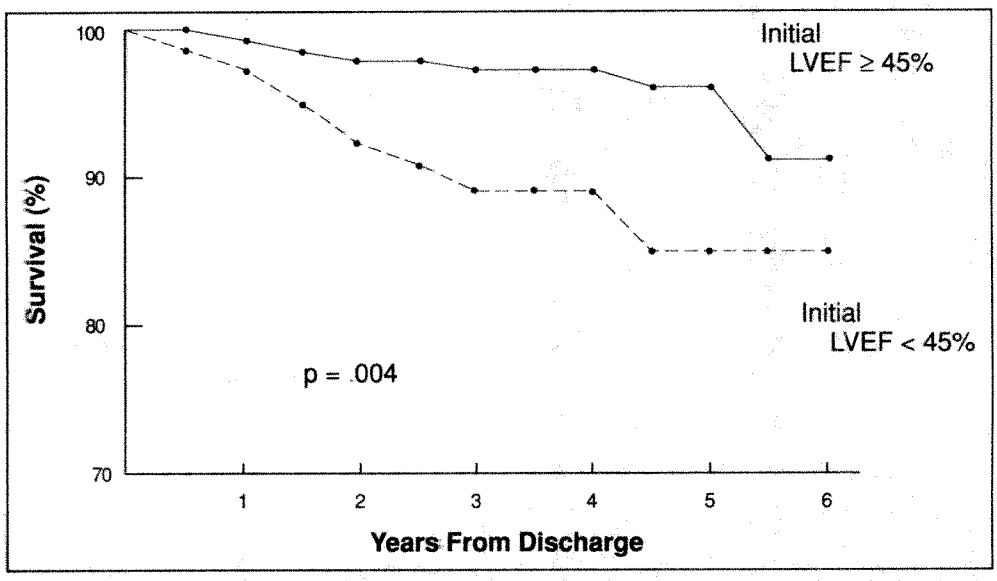


FIGURE 2. Kaplan-Meier survival curves for 224 patients with initial left ventricular ejection fraction (LVEF) ≥45% versus 81 patients with initial LVEF <45%.

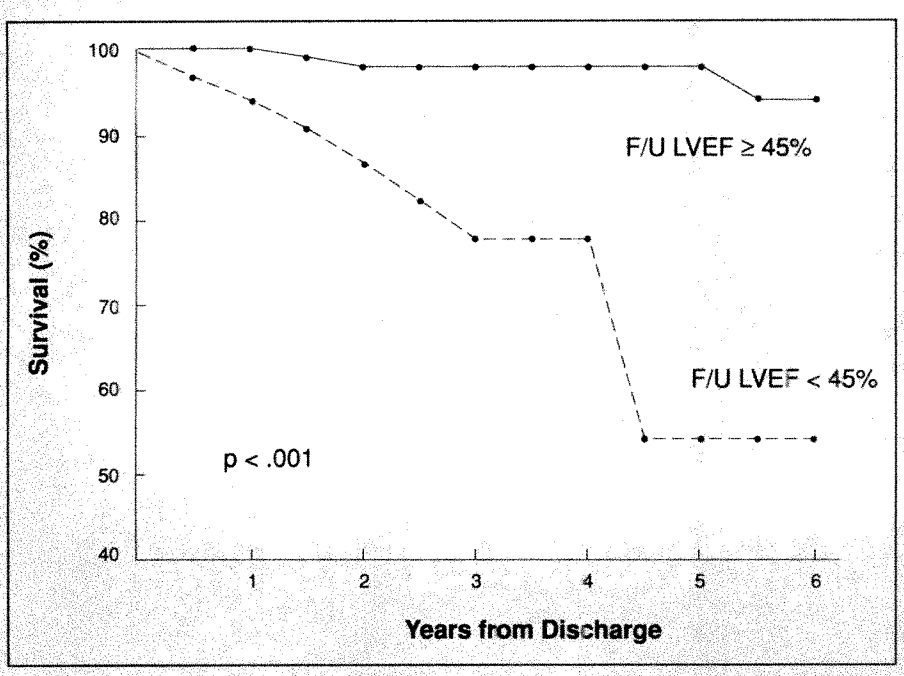


FIGURE 3. Kaplan-Meier survival curves for 163 patients with follow-up left ventricular ejection fraction (F/U LVEF) ≥45% versus 33 patients with F/U LVEF <45%.

LVEF on late cardiac mortality is illustrated in Figure 4.

Patency of the infarct-related artery and late cardiac mortality: The baseline characteristics of the 348 hospital survivors with patent and occluded IRAs are listed in Table IV. The 2 groups were similar in most baseline characteristics. Patients with a patent IRA had better recovery of LV function than patients with an occluded IRA (follow-up LVEF 58.5 ± 13% vs 46.7 ± 13%, p <0.001). There was no significant difference in late cardiac mortality between patients with a patent IRA and patients with an occluded IRA (15 of 317 or 4.7% vs 2 of 31 or 6.5%, p = 0.67). Figure 5 compares the survival curves for the 2 groups.

In 81 patients with depressed initial LVEF <45%, the late cardiac mortality in patients with a patent IRA was lower than in patients with an occluded IRA (7 of 76 or 9.2% vs 2 of 5 or 40%, p = 0.03). Patients with a patent IRA had better recovery of LV function than patients with an occluded IRA (follow-up LVEF 47.3 ± 13% vs 33.0 ± 13%, p <0.04). When differences in late cardiac mortality between patent and occluded infarct artery groups were adjusted for differences in follow-up LVEF, patency was no longer a significant predictor of late cardiac mortality.

In the small subgroup of patients with 1-vessel coronary disease and depressed follow-up LVEF <45%, there were 2 late cardiac deaths (50%) among 4 patients with an occluded IRA compared with no late cardiac deaths among 7 patients with a patent IRA (p <0.04).

TABLE IV Demographic and Angiographic Characteristics According to Patency of the Infarct-Related Artery at Hospital Discharge

Variable	Patent IRA no. (%) (n = 317)	Occluded IRA no. (%) (n = 31)	p Value
Age (year ± SD)	58.4 ± 11	58.5 ± 11	NS
Men	234 (73.8)	21 (67.7)	NS
Prior AMI	60 (18.9)	11 (35.5)	0.03
Prior CABG	8 (2.5)	1 (3.2)	NS
Cardiogenic shock	10 (3.2)	1 (3.2)	NS
Anterior wall AMI	138 (43.5)	13 (41.9)	NS
Late reperfusion (>6 hours)	37 (11.7)	3 (9.7)	NS
Multivessel coronary disease	166 (52.4)	9 (29.0)	0.01
Initial LVEF (% ± SD)	53.6 ± 13	52.8 ± 10	NS
Follow-up LVEF (% ± SD)	58.5 ± 13	47.6 ± 13	<0.001

Abbreviations as in Tables II and III.

DISCUSSION

This study was designed to test the hypothesis that a patent IRA is a predictor of hospital and late cardiac survival, independent of its effect on preservation of LV function. Our results indicate that a patent IRA is the most important determinant of hospital survival, and that follow-up LVEF is the most important determinant of late cardiac survival. Patency is not a predictor of late cardiac survival in the group of hospital survivors as a whole, but does appear to be important for late survival in patients with depressed initial LVEF. In this subgroup, patency appears to enhance late cardiac survival primarily by its effect on preservation of LV function. Patients with patent arteries had substantial recovery of LV function, whereas patients with occluded arteries did not, and when late cardiac survival was adjusted for differences in recovered LV function, patency was no longer a predictor of late cardiac survival.

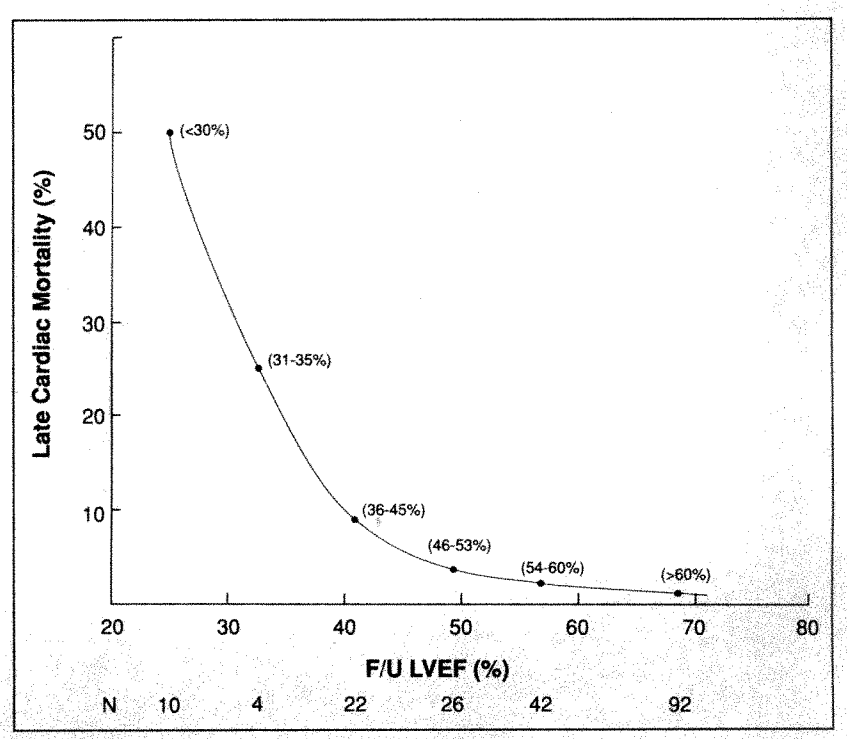


FIGURE 4. Late cardiac mortality rate in 6 categories of follow-up left ventricular ejection fraction (F/U LVEF). The coordinates of each point shown on the graft represent the mean F/U LVEF and the mortality rate for each category. Number of patients in each category, and the range of F/U LVEF for each category is shown in *parentheses*.

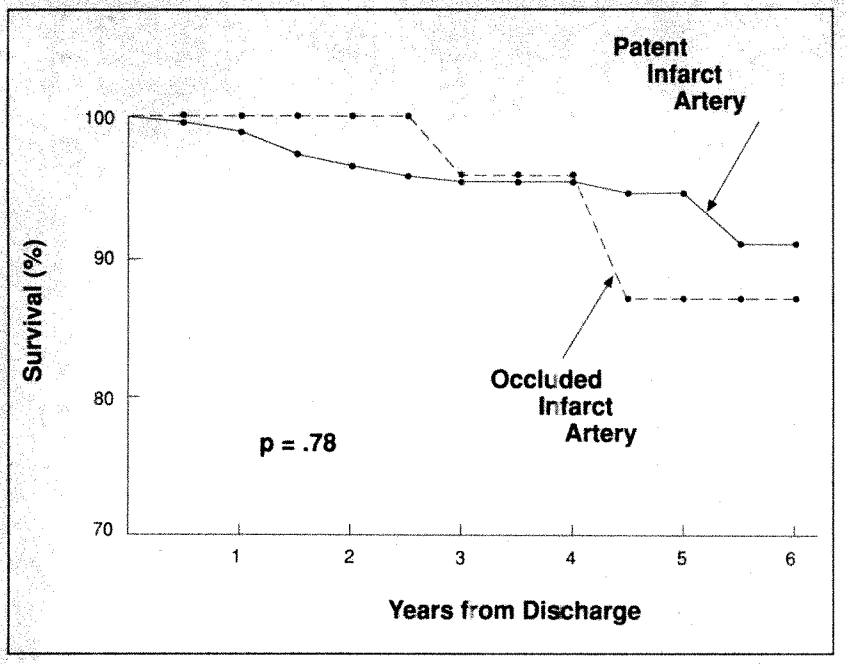


FIGURE 5. Kaplan-Meier survival curves for 317 patients with patent infarct arteries versus 31 patients with occluded infarct arteries at hospital discharge.

Studies supporting the open artery hypothesis: Numerous studies have documented the importance of a patent IRA for hospital survival,[6,10–12] but the evidence that a patent IRA is important for late survival, independent of its effect on preservation of LV function, has been conflicting.[5,13,14] The strongest evidence in support of the importance of a patent IRA for late survival comes from the Western Washington trial.[5] This trial, in which patients were treated relatively late with intracoronary streptokinase, found improved late survival in patients discharged with a patent IRA despite the fact that there was no improvement in LV function. Additional evidence comes from Cigarroa et al,[15] who found that a patent IRA resulting from spontaneous reperfusion after AMI was associated with a striking survival benefit in hospital survivors with 1-vessel disease despite the fact that these patients had no improvement in LV function.

Several possible explanations have been proposed as to why a patent IRA may be important for late survival independent of its effect on preservation of LV function.[3,4] Late reperfusion may prevent LV remodeling and expansion even when it is too late to salvage myocardium.[16–18] An open infarct artery may also improve electrical stability and may provide a conduit for collateral vessels in the event of subsequent occlusion of a contralateral coronary artery.[19,20]

Studies refuting the open artery hypothesis: Despite these potential benefits, other studies appear to refute the open artery hypothesis. The Interuniversity Cardiology Institute of the Netherlands Trial, in which patients with AMI were treated with intracoronary streptokinase, found improved late survival in patients with an open versus a closed infarct vessel, but the differences disappeared when patients were stratified by LVEF.[14] This study suggested that the survival benefit after thrombolytic therapy was due to myocardial salvage and that there was no independent survival benefit of an open artery.

Comparison with our results: Our results are similar to the Interuniversity Cardiology Institute of the Netherlands Trial but differ from the Western Washington Trial. One possible explanation for the differences between our results and those of the Western Washington Trial may be related to the type of reperfusion strategy used. In our study coronary angioplasty was performed to establish reperfusion and additional revascularization procedures were performed in patients with recurrent ischemia and in patients with high-risk coronary anatomy. Consequently, many patients who otherwise would have been discharged with an occluded IRA were converted to an open artery. For example, 12 of 23 patients with in-hospital reinfarction underwent repeat successful emergency coronary angioplasty and left the hospital with an open artery. Also, 7 of 22 hospital survivors with initial unsuccessful angioplasty underwent coronary bypass surgery for multivessel coronary disease and left the hospital with an open artery. This has the effect of removing these high-risk patients from the occluded artery group and lowering the mortality in the occluded artery group.

We did find a small subgroup of hospital survivors (patients with 1-vessel coronary disease and depressed follow-up LVEF) in which patency may have had an independent effect on late cardiac survival. The numbers are very small and we cannot draw any firm conclusions, but our data suggest that subgroups may exist in which patency of the IRA is important for late survival independent of its effect on preservation of LV function.

Study limitations: The present study is limited by the relatively small number of patients with occluded IRAs at hospital discharge and the small number of late cardiac deaths. The small numbers may make it diffi-

cult to detect significant differences in late cardiac survival between patients with patent and occluded infarct arteries, and the small numbers also limit subgroup analyses. Another limitation of our study is that follow-up angiographic data were obtained in only 63% of hospital survivors. Patients with follow-up angiography had a higher incidence of anterior myocardial infarction (50 vs 35%, $p = 0.005$), were younger (57 ± 11 vs 60 ± 11 years, $p = 0.003$), and had lower initial LVEF ($52.4 \pm 13\%$ vs $55.3 \pm 13\%$, $p = 0.05$) than those without follow-up angiography. It is possible that this selection bias could affect our results.

Clinical implications: Our study indicates that patency of the IRA is the most important determinant of hospital survival after direct angioplasty for AMI. Patency of the IRA may also be important for late cardiac survival in patients with depressed initial LVEF, but this appears to be related primarily to the effects of patency on recovery of LV function. LV function (measured after recovery) is the most important determinant of late cardiac survival after direct angioplasty, just as it is after conventional therapy for AMI.[21] Reperfusion strategies that produce the highest patency rates of the IRA and allow the maximal recovery of LV function should provide the best hospital and late cardiac survival. In our study population, the aggressive management of recurrent ischemia with additional revascularization procedures may contribute to the very low late cardiac mortality.

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Evaluation of a Prolonged Infusion of Recombinant Tissue-Type Plasminogen Activator (Duteplase) in Preventing Reocclusion Following Successful Thrombolysis in Acute Myocardial Infarction

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The hypothesis that an infusion of recombinant tissue-type plasminogen activator (rt-PA) maintained for up to 24 hours could prevent reocclusion after early coronary patency had been established was evaluated in patients with acute myocardial infarction. The rt-PA studied was an investigational double chain rt-PA (Duteplase®, Burroughs Wellcome Co.), administered according to body weight. Coronary patency was documented in 139 of 213 patients who had 90-minute angiograms recorded after an initial lytic dose of rt-PA. In these responders a further 90-minute infusion at one third the initial lytic dose was given before assignment to 1 of 4 maintenance dose rates (0.012, 0.024, 0.036, 0.048 MIU/kg/hour) which were continued for the subsequent 9 to 21 hours. The principal end point was the status of the infarct-related coronary artery 12 to 24 hours after the start of therapy, and before termination of rt-PA, in patients with initially patent vessels at 90 minutes.

Of the 103 responders with repeat angiograms after a 9 to 21 hour maintenance infusion of rt-PA, a total of 17 (16.5%) patients reoccluded across all doses administered. There was no significant relationship between the maintenance dose rate and the incidence of reocclusion. However, there was strong association between total dose of rt-PA administered and the incidence (16%) of serious or life-threatening bleeding exclusive of surgery. Other factors associated with serious bleeding included low body weight, female gender, and total duration of rt-PA infusion. Reocclusion was independent of the 90-minute Thrombolysis in Myocardial Infarction trial perfusion grade and diameter of infarct vessel. Rethrombosis after establishment of early patency after rt-PA remains a significant problem that is unaffected by sustained rt-PA infusion in doses that can be tolerated.

(Am J Cardiol 1992;69:1120–1127)

Reocclusion of the infarct artery after initially successful thrombolysis in acute myocardial infarction remains a significant obstacle to preserving myocardial salvage. Marder and Sherry[1] suggested that rethrombosis after reperfusion occurs in inverse proportion to the plasma half-life of the thrombolytic agent used. In the case of recombinant tissue-type plasminogen activator (rt-PA), the drug's short half-life (3 to 5 minutes) has stimulated investigations of maintenance infusions for up to 6 hours after establishing patency of the infarct artery. Two randomized angiographic studies evaluating the efficacy of heparin versus heparin plus rt-PA as maintenance infusions have yielded conflicting results. Verstraete et al[2] found no benefit from a 6-hour infusion of 30 mg of rt-PA after initial patency was demonstrated with 40 mg of rt-PA. Johns et al[3] found a reduction in reocclusion with a 4-hour rt-PA infusion of 0.8 mg/kg after coronary patency was established following a lytic dose of 1 mg/kg.

We hypothesized that the infusion of a novel rt-PA (Duteplase®, Burroughs Wellcome Co.) maintained for up to 24 hours, could prevent reocclusion. Several maintenance doses of rt-PA were evaluated to identify the optimal hourly dose rate to prevent reocclusion. The dose of rt-PA in this study was administered according to patients' body weight in an effort to minimize bleeding complications. The principal end point was the status of the infarct-related coronary artery 12 to 24 hours after initiation of therapy, and before termination of rt-PA in those with initially patent vessels 90 minutes after therapy began. In addition, the efficacy of rt-PA given intravenously over 90 minutes in achieving coronary artery perfusion in patients with acute myocardial infarction and the safety of prolonged infusions of rt-PA were also evaluated. Finally, a quantitative analysis of the severity of stenosis in the infarct-related artery was per-

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formed to establish the predictive value of this measurement in estimating reocclusion risk in those arteries initially patent.

METHODS

This was an open, parallel, multicenter trial. The protocol and consent form were approved by the appropriate Institutional Review Board of each of the eleven participating institutions (see Appendix 1).

Study population: Patients were recruited from 11 participating North American centers over a 14-month period beginning July 24, 1986. Of the 223 patients entered into the study 183 were men and 40 were women (mean age of 54.5 years). There were 104 patients with anterior, 118 with inferior myocardial infarctions and 1 patient was subsequently determined not to have had a myocardial infarction.

Patients had to meet the following criteria to be eligible for the trial: age ≤75 years, ischemic chest pain consistent with myocardial infarction lasting ≥30 minutes, in association with new ST-segment elevation of ≥2 mm in 2 inferior leads or in lead 1 and aVL, or 3 mm in ≥2 anterior precordial leads; and completion of all screening procedures within 6 hours of the onset of chest pain.

Exclusion criteria included the following: cardiogenic shock if systolic pressure could not be increased to 80 mm Hg with vasopressors, left bundle branch block, previous aortocoronary bypass surgery, and obvious contraindications to thrombolytic therapy.

Thrombolytic therapy: The rt-PA (Duteplase) used in this study differs from alteplase by having a substitution of methionine for valine at amino acid position 245 in the Kringle 2 region. Duteplase also differs by having a specific activity (units of thrombolytic activity per mg protein) of 310,000 IU/mg compared with 580,000 IU/mg for alteplase, and by existing in a double-chain rather than a predominantly single-chain form. For the purpose of this study, dose was expressed in units of thrombolytic activity designated MIU (million International Units by a clot lysis assay). This rt-PA preparation has been previously shown to produce improvement in global and infarct regional left ventricular function in acute myocardial infarction (4) and to have a similar effect on mortality as streptokinase in the International Study of Infarct Survival-3 study.[5]

An initial 90-minute infusion (lytic dose) of Duteplase was administered to 223 eligible patients with suspected AMI a mean of 3.4 hours (SD = 1.0 hour, range 1 to 6 hours) from symptom onset. The goal of the first 90-minute infusion was to establish coronary artery patency upon which the influence of a maintenance rt-PA infusion on reocclusion could be evaluated. In the first 45 patients, 0.3 MIU/kg was infused over 90 minutes as the lytic dose. After initial evaluation of the efficacy of this dose in producing 90-minute patency, the dose was increased to 0.42 MIU/kg over 90 minutes for the subsequent 178 patients.

If perfusion of the infarct-related coronary artery was judged grade 2 or of the 3 Thrombolysis in Myocardial Infarction Trial (TIMI), the patient was considered a responder at 90 minutes and was given one third of the initial dose for the subsequent 90 minutes. After these 2 consecutive 90-minute infusions of rt-PA, responders were then given a continuous maintenance infusion of 0.012, 0.024, 0.036, or 0.048 MIU/kg/hour for the subsequent 9 to 21 hours. The assignment of maintenance dose was made centrally at Burroughs Wellcome Co. to balance the number of patients receiving each dose and to evaluate the safety of lower doses across centers before proceeding to higher doses. A repeat angiogram was recorded between 12 and 24 hours after rt-PA was begun and the infusion was discontinued after the repeat angiogram.

Toward the end of this study, it became apparent that the incidence of serious bleeding (largely confined to the site of intravascular instrumentation) with prolonged rt-PA infusions was higher than that in studies of shorter infusions. For this reason, the protocol was amended so that the last 25 patients studied received a shortened maintenance infusion of 3 hours (i.e., a reduced total period of rt-PA administration of 6 hours). These patients still had their repeat angiograms recorded at 12 to 24 hours with a drug-free period before their repeat angiogram. Because the original purpose of the study was to evaluate reocclusion when a maintenance infusion of rt-PA was maintained through a repeat angiogram, the subset of 25 patients who received only 6 hours of rt-PA were analyzed separately for their incidence of reocclusion.

Concomitant therapy: Lidocaine 1.0 to 1.5 mg/kg was given as a bolus before administration of rt-PA, and a lidocaine infusion of 2 mg/min was maintained for 48 hours. An intravenous bolus of heparin (5,000 IU) was administered at the time of the initial cardiac catheterization in all patients. A continuous infusion of heparin (1,000 IU/hour) was begun immediately after the 90-minute angiogram in responders and continued for 72 hours. The heparin infusion rate was adjusted to maintain the partial thromboplastin time approximately twice control. Aspirin therapy was not required by protocol but was recommended before discontinuation of heparin.

Clinical course: All patients were monitored clinically and electrocardiographically. Special attention was directed toward bleeding complications, monitoring of hematologic indexes, and transfusion requirements. Serious bleeding was defined as bleeding from any source severe enough to require blood transfusion or to affect clinical status significantly.

Percutaneous transluminal coronary angioplasty was allowed at the discretion of the attending physician in nonresponders at 90 minutes and in responders at the end of repeat coronary angiography following completion of the maintenance infusion of rt-PA. Angioplasty was not permitted during rt-PA infusion in responders unless they had symptomatic recurrent ischemia.

Coagulation studies: In a subset of patients, blood was collected in tubes containing 3.8% citrate and either 200 KIU/ml aprotinin or polyclonal antibody to rt-PA at baseline, 90 minutes, and at 4, 12, 24 and 48 hours. Fibrinogen was quantified using the sulfite precipitation

assay.[6] Fibrinogen degradation products were measured by a modified Thrombo-Wellcotest method.

Angiographic assessment: Angiographic data were independently evaluated through consensus reading of 2 experienced observers at a core laboratory at the University of Washington in Seattle. The evaluators had no knowledge of the clinical status of the patients or of rt-PA dose. A TIMI perfusion grade[7] was assigned for the 90-minute angiogram, and a second perfusion grade was assigned for patients who underwent repeat angiography after administration of one of the assigned rt-PA maintenance infusion regimens. Quantitative angiography was performed by projecting the 90-minute images at high magnification and manually digitizing the lumen borders of the infarct lesion with subsequent digitization from the best view.[8] Lesion measurements included lumen diameter at the point of greatest narrowing of the densely opacified recanalized lumen and percent diameter reduction.

Data analysis: Efficacy results were analyzed using perfusion grades determined by the core angiographic laboratory with the exception of 6 patients who underwent an emergency repeat catheterization and had only local data for their second angiogram. Bleeding was summarized by the number of patients with at least 1 episode of serious, life-threatening or fatal bleeding. Data analysis involved the use of Fisher's exact test, Cochran-Mantel-Haenszel rank correlation test, and logistic regression analysis as appropriate. All p values reported are 2-tailed.

RESULTS

In Figure 1 a summary of study treatments and outcomes including angiographic results is provided. Ten patients who had either no core laboratory reading for a 90-minute angiogram (9 patients) or did not have the disease of interest (1 patient) were excluded from the analysis of 90-minute patency.

The angiographic core laboratory unaware of the clinical characteristics determined that 139 patients had TIMI perfusion grade 2 or 3 (responders) at 90 minutes. The response rate in the first 45 patients who received a 90-minute lytic infusion of 0.30 MIU/kg was 56% (95% confidence interval [CI] 40 to 71%) and the response rate in the subsequent 178 patients who received 0.42 MIU/kg was 68% (95% CI 60 to 74%) (p = not significant).

In 11 of the 139 responders, repeat angiograms were unavailable. Of the 128 responders with repeat angiography, 103 had the long (9 to 21 hours) maintenance infusion and 25 had the short (3 hours) maintenance infusion. Urgent angiography earlier than scheduled was performed in 5 patients who received the long infusion and in 1 patient who had the short infusion. Of the patients with early unscheduled angiography, 4 had urgent catheterization for suspected reocclusion, 1 had

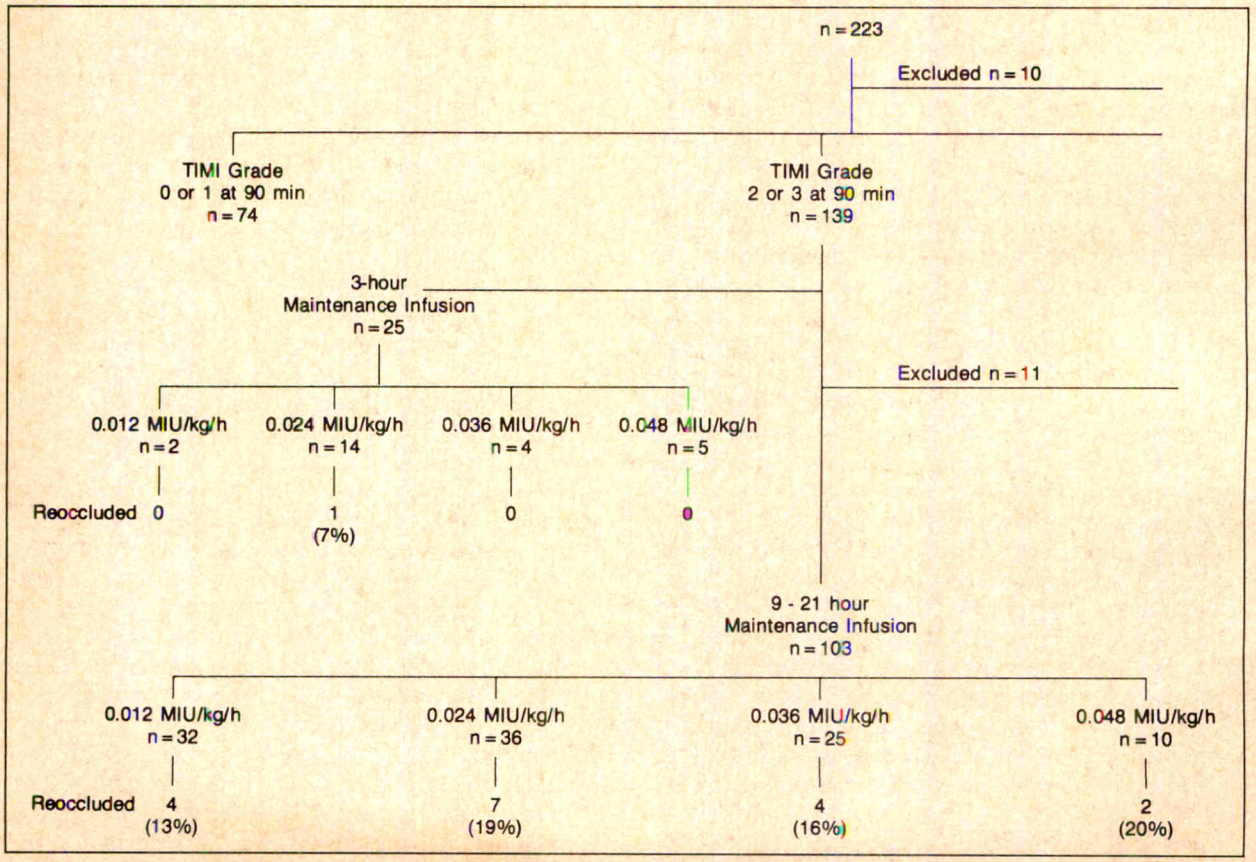


FIGURE 1. Flow diagram of patient accountability and angiographic results. Number of patients are shown numerically; maintenance infusion rates of recombinant tissue-type plasminogen activator (rt-PA) are shown in MIU/kg/hour. TIMI = Thrombolysis in Myocardial Infarction trial.

temporary cardiopulmonary resuscitation for cardiac arrest, and another had bleeding that led to termination of the infusion. These patients were all included in the analysis of reocclusion.

Mean duration of the maintenance infusion (beginning 3 hours after the initiation of rt-PA) in the long infusion group was 14.2 hours (SD = 4.7 hours), and in the short infusion group 3.1 hours (SD = 0.2 hour). The number and percentage of patients in whom reocclusion occurred in each maintenance dose group are also shown in Figure 1. A Cochran-Mantel-Haenszel rank correlation test revealed no significant relation between maintenance dose rate and the rate of reocclusion in the long or short infusion group. Across all doses, 17 or 16.5% (95% CI 10 to 25%) of patients receiving the long maintenance infusion, and 1 of the 25 or 4% (95% CI 0 to 20%) receiving the short maintenance infusion had reocclusion ($p = 0.20$).

Factors that may have influenced the rate of reocclusion: Patients who received a long maintenance infusion are classified as to whether they had reocclusion or remained patent after rt-PA infusion in Figure 2, and then compared according to their initial lytic dose, total dose and length of maintenance infusion. There was no apparent association between risk of reocclusion and any of these variables.

In Figure 3, the impact of the initial perfusion status of the infarct-related coronary artery as assessed by TIMI perfusion grade and quantitative coronary angiography is depicted according to whether patients had reocclusion despite a maintenance infusion or remained patent. Again, there was no difference as it related to any of these parameters, nor did the risk of reocclusion vary according to which coronary artery was involved.

Coagulation data: In Table I a summary of fibrinogen values (sulfite precipitation method) is provided in the subset of 73 patients who had plasma collected in the presence of aprotinin or polyclonal antibody to rt-PA to prevent in vitro artifact.

In Table II a summary of fibrinogen degradation product values ($\mu g/ml$) is provided in the subset of 75 patients who had plasma collected in the presence of aprotinin or polyclonal antibody to rt-PA. For almost all of the patients, only mild elevation of fibrinogen degradation products occurred between 90 minutes and 12 hours.

Bleeding: No patients experienced bleeding which resulted in death and there were no instances of central nervous system bleeding. At least 1 unit of blood for serious bleeding exclusive of surgery was required in 16% of patients (35 of 223). The transfusion requirement was related almost entirely to bleeding at sites of intravascular instrumentation. Patients who required transfusion had a significantly lower average body weight (76.5 kg) than those who did not require transfusion (82.5 kg, $p < 0.05$). In addition, the proportion of women requiring transfusion (14 of 40, 35%, 95% CI 20 to 50%) was significantly greater than the proportion of men requiring transfusion (21 of 183, 11%, 95% CI 7 to 16%; $p < 0.01$). In a logistic model in which gender is the only predictor, the odds ratio for the association of female sex with serious life-threatening bleeding is 2.78 (95% CI 1.28 to 6.06). When total dose, infusion duration and body weight are also controlled for, the odds ratio is 2.59 (95% CI 1.04 to 6.48). In the subset of patients with fibrinogen measured in the presence of an inhibitor of in vitro artifact, those with serious bleeding (n = 10) tended to have a slightly lower mean minimal

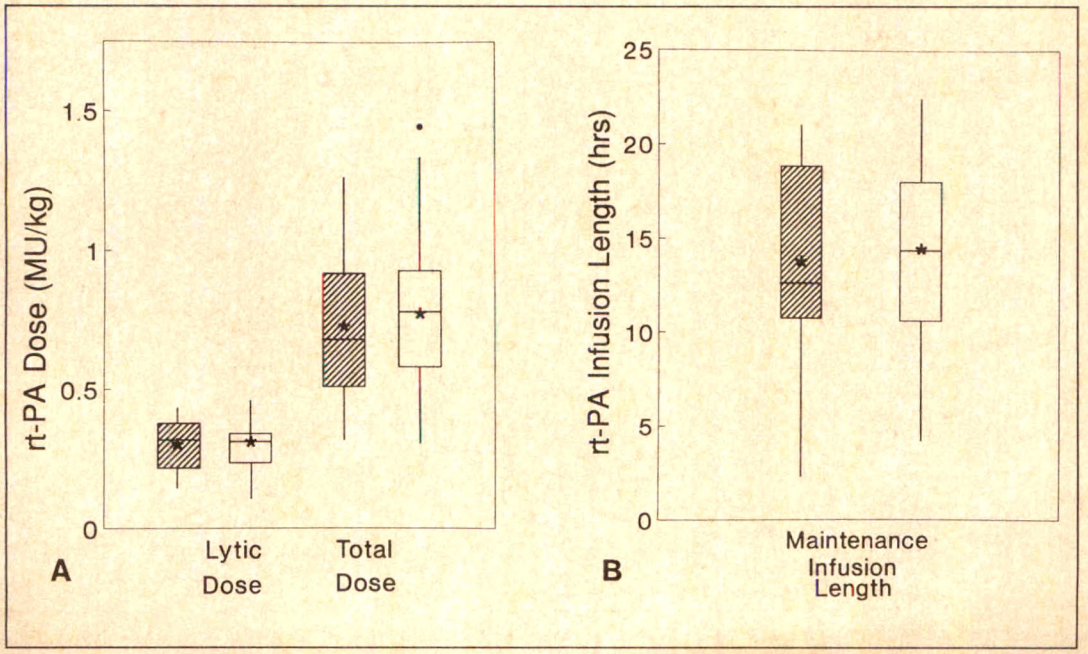


FIGURE 2. ***A*, impact of dose of recombinant tissue-type plasminogen activator (rt-PA) infusion on risk of reocclusion. Data are represented in *box and whisker* format. Patients who received a long maintenance infusion and had reocclusion (n = 17) are indicated by *hatched boxes;* patients who had residual patency of infarct-related coronary arteries (n = 86) are indicated by *open boxes. B*, impact of length of rt-PA infusion on risk of reocclusion. Data are represented as in Figure *A*.**

TABLE I Percent Baseline of Fibrinogen Remaining

Scheduled Time	No. of Pts.	
Baseline	73	393 ± 12.8 mg/dl
90 minutes	67	92 ± 1.8%
4 hours	68	88 ± 2.4%
12 hours	66	76 ± 2.1%
24 hours	64	77 ± 2.9%
48 hours	60	100 ± 3.4%

Data represent mean ± SEM for baseline and percent remainder for all subsequent times.

TABLE II Summary of Fibrinogen Degradation Products (μg/ml)

Scheduled Time	No. of Pts.	Minutes	25th Percentile	Median	75th Percentile	Maximum
Baseline	75	10	10	10	10	20
90 minutes	69	10	10	20	40	640
4 hours	70	10	10	40	80	320
12 hours	68	10	10	10	40	320
24 hours	66	10	10	10	20	160
48 hours	60	10	10	10	10	640

fibrinogen value between 90 minutes and 48 hours than did patients without serious bleeding (n = 61) (244 vs 276 mg/dl, p = 0.22).

Figure 4A depicts the relation between total does of rt-PA and the percentage of patients with serious or life-threatening bleeding complications. Figure 4B illustrates the relation between infusion duration and percentage of patients with serious or life-threatening bleeding complications. Total dose of rt-PA and infusion duration were highly correlated variables (p < 0.001), and both were associated with an increased risk of serious or life-threatening bleeding (p <0.001). A logistic regression model was used to evaluate the relative contributions of total dose and infusion duration to the incidence of serious and life-threatening bleeding. After adjustment for the contribution of total dose, infusion duration still contributed significantly to the prediction of serious and life-threatening bleeding (p <0.01). There was, however, no significant contribution of total dose to these events after adjustment for the contribution of infusion duration.

Percutaneous coronary angioplasty: Of the 108 patients who underwent percutaneous coronary angioplasty during hospital admission, 42 of the 74 nonresponders (57%) had percutaneous coronary angioplasty, compared with 66 of the 139 responders (47%). Percutaneous coronary angioplasty was not permitted in responders until the time of repeat catheterization unless they were clinically unstable. An additional 34 patients underwent coronary artery bypass surgery: 4 patients (5%) with TIMI 0 or 1 at 90 minutes underwent coronary artery bypass graft surgery, compared with 30 patients (22%) with TIMI 2 or 3 at 90 minutes.

Mortality: During hospitalization, 20 patients (9.0%) died. No significant difference occurred in the death rate between responders (10 of 139 or 7.2%) and nonresponders (7 of 74 or 9.5%).

DISCUSSION

The principal novel findings in this study are: (1) Reocclusion is not prevented by sustained rt-PA maintenance infusions over a wide dose range. (2) A patency rate of 68% was demonstrated after a 90-minute continuous infusion of double chain rt-PA (Duteplase, Burroughs Wellcome) in a dose of 0.42 MIU/kg. (3) A

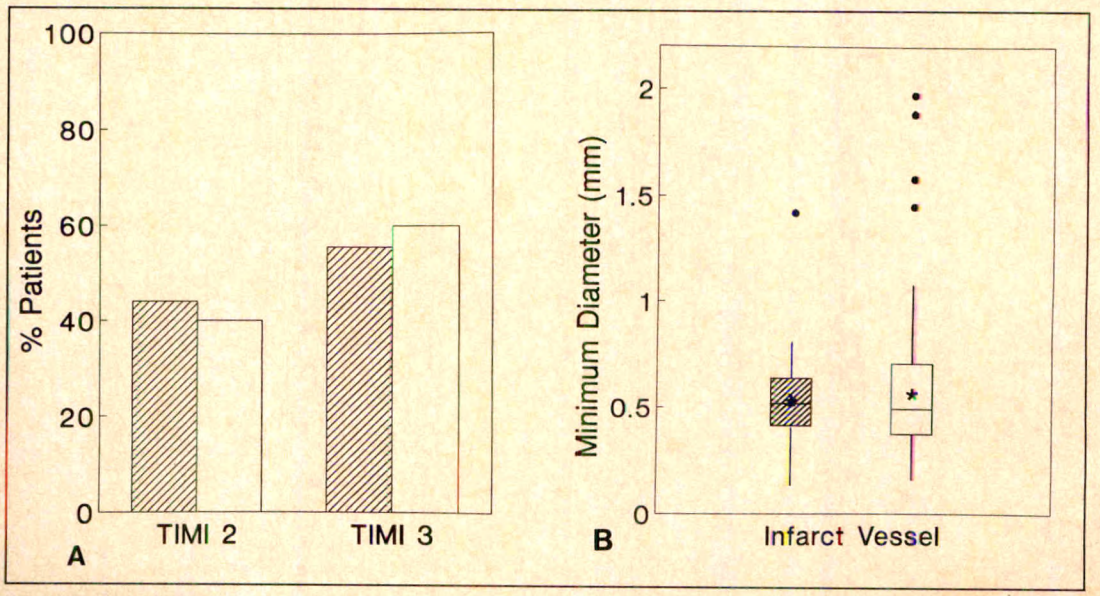


FIGURE 3. ***A*, impact of initial coronary perfusion status assessed by Thrombolysis in Myocardial Infarction Trial (TIMI) grade and determined at 90 minutes after onset of recombinant tissue-type plasminogen activator (rt-PA) infusion on risk of reocclusion. Patients who had reocclusion (n = 17) are indicated by *hatched bars;* patients who had residual patency of infarct-related coronary arteries (n = 86) are indicated by *open bars. B*, impact of initial minimal diameter of infarct-related coronary artery determined at 90 minutes after onset of rt-PA infusion on risk of reocclusion. Data are represented in *box and whisker* format. Patients who had reocclusion (n = 17) are indicated in *hatched boxes;* patients who had residual patency of infarct-related coronary arteries (n = 86) are indicated in *open boxes.***

clear relationship between both total dose and duration of infusion of rt-PA on serious and life-threatening bleeding complications was seen.

Reocclusion: To assess reocclusion, this study used a maintenance infusion of rt-PA of a longer duration than any study reported, and the infusion was maintained throughout a repeat angiogram. However, in the dose range studied, it was not possible to prevent infarct artery reocclusion. Contrary to some previous reports, but in agreement with others, it did not appear that either the TIMI perfusion grade or minimal diameter of the infarct vessel influenced the risk of reocclusion.[9,10] Although the final 25 patients studied with a short maintenance infusion were not evaluated in a randomized manner but rather studied sequentially, as mandated by the protocol amendment, their incidence of reocclusion was small, i.e., 4%, and comparable to that reported by Johns and co-workers[3] in a series of 25 patients who were treated with a 4-hour maintenance rt-PA infusion after patency was established with a lytic dose. Although caution should be exercised in comparing the short and long maintenance infusion groups in our study, the possibility exists that a long maintenance infusion actually accentuated rather than attenuated the propensity for coronary reocclusion.

If continuing thrombolysis is a requirement for the prevention of reocclusion, why were we unable to show evidence for prevention of reocclusion in our study? It is now appreciated that residual thrombus following thrombolytic therapy is a strong thrombogenic stimulus that leads to both an increase in platelet aggregation and thrombin activity.[11] It is conceivable that the maintenance infusion of rt-PA in this study was associated with re-release of clot-bound thrombin, potentiating the formation of new clot. Maintenance doses of rt-PA higher than those used in this study may have been more successful in lysing this new clot, but would likely be associated with a higher incidence of hemorrhagic complications, given the association between total dose of rt-PA and serious bleeding.

A variety of local and systemic factors, unmeasured in the current study, may be additional modulators of an individual patient's propensity to reocclude the infarct-related coronary artery after successful thrombolysis. These include denudation of the infarct-related coronary artery at the site of plaque fissuring with subsequent collagen exposure, residual thrombus and distal embolization, and reperfusion injury to coronary artery endothelium. Intraplaque hemorrhage aggravated by a long infusion of rt-PA also might have contributed to a higher likelihood or reocclusion. Vasospasm mediated either locally or systemically may also be operative.[12] Unmeasured indicators of coagulation activity such as fibrinopeptide-A might have yielded additional insights into reocclusion in this study.[13]

Thrombolytic efficacy, bleeding and coagulation factors: The thrombolytic efficacy of this new double-chain rt-PA preparation compares favorably with that previously reported for rt-PA. Likewise, the propensity for significant bleeding and transfusion requirements, at least in patients requiring intravascular cannulation, is comparable to other studies. Total dose and especially the duration of rt-PA infusion in this study were predictors of serious bleeding. High doses of rt-PA and long infusions could contribute to an extravascular deposition of rt-PA, thereby prolonging its effect. Similarly, increased duration of rt-PA exposure to the endothelium and platelets may contribute to occupancy of a larger proportion of rt-PA–binding sites on both endothelial and platelet surfaces. Although there was a substantial incidence of serious bleeding in this study, it was considered life-threatening in only 1 patient. Moreover, there was no central nervous system bleeding; in most instances of serious bleeding, the sites were related to vas-

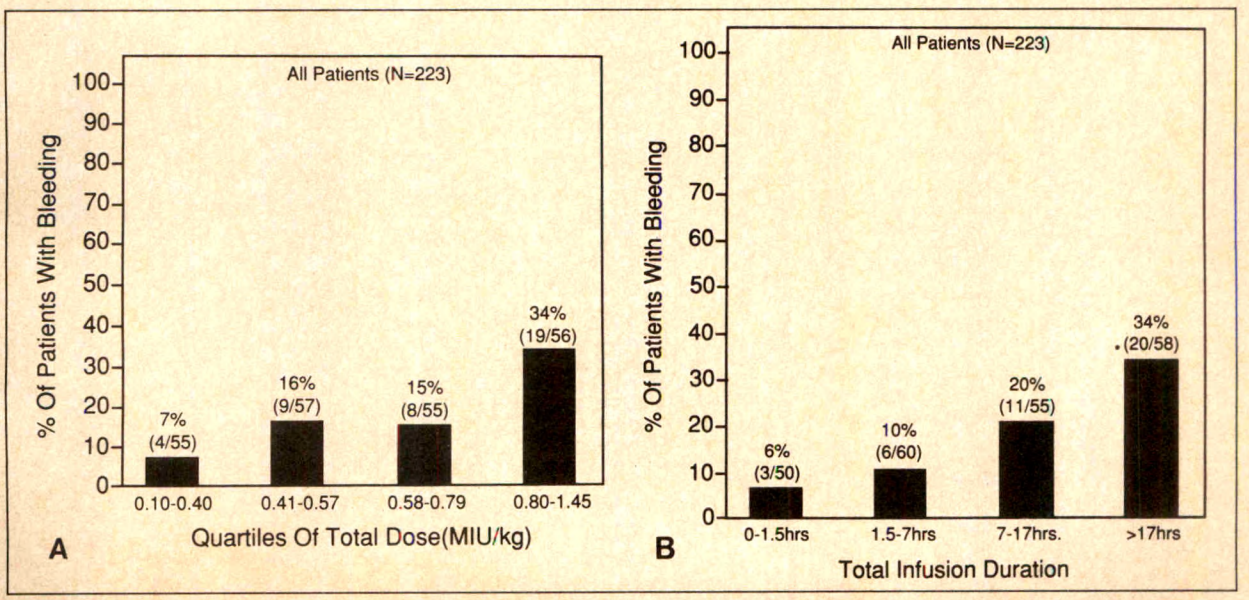


FIGURE 4. Relation between total dose of recombinant tissue-type plasminogen activator (rt-PA) and percentage of patients (n = 223) with serious or life-threatening bleeding complications (p <0.001). Patients are assigned by quartiles of rt-PA total dose (MIU/kg). *B*, relation between total rt-PA infusion duration and percentage of patients (n = 223) with serious or life-threatening bleeding complications (p <0.001).

cular cannulation mandated by the study protocol. In concert with previous reports and despite dosing by body weight, the female gender proved to be an independent risk factor for hemorrhage.[14,15] Although differences in tissue turgor might account for the hemorrhagic predilection in women, the basis for this finding remains unclear and is worthy of further investigation.

Despite infusions of rt-PA for up to 24 hours in this study, fibrinogen was relatively well preserved, and fibrinogen degradation products increased only moderately.

Rethrombosis after establishment of early patency after rt-PA remains a significant problem which is unaffected by sustained rt-PA infusion in doses that can

APPENDIX—Clinical Sites

Investigator(s)	Study Nurse	Institution
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Paul W. Armstrong, MD (PI) Rudolph Canepa-Anson Luigi Casella Robert Chisholm Michael Freeman	Christine Beck, RN	St. Michael's Hospital, Toronto, Canada
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James Perry Jr., MD (PI) Mervyn B. Forman, MD	Rita Chesley, RN	Vanderbilt University Nashville, TN
James F. Spann, MD (PI)	Colleen Neal, RN	Medical University of S. Carolina Charleston, SC
George Vetrovec, MD (PI)	Ginger Edwards, RN, FNP Sharon Cole, RN	Medical College of Virginia Richmond, VA
	Core Laboratories	
Angiographic Core Laboratory Florence Sheehan Greg Brown	University of Washington School of Medicine Seattle, Washington	
Hematology Core Laboratory Philip C. Comp, MD, PhD Toppy Nelson	University of Oklahoma Health Sciences Centre Oklahoma City, Oklahoma	

be tolerated. Future strategies using other techniques such as adjunctive therapy with specific antithrombin agents deserve exploration.

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Differential Long-Term Impact of In-Hospital Symptoms of Psychological Stress After Non-Q-Wave and Q-Wave Acute Myocardial Infarction

Nancy Frasure-Smith, PhD, François Lespérance, MD, and Martin Juneau, MD

Because of their unstable pathophysiology, it was hypothesized that patients with non-Q-wave acute myocardial infarctions (AMI) would be more vulnerable to the negative effects of psychological stress than patients with Q-wave AMI, and thus would be more likely to benefit from programs aimed at relieving stress. This hypothesis was tested through secondary analysis of data from a 1-year randomized clinical trial of psychological stress monitoring and intervention after AMI. After discharge, treatment group patients were telephoned each month and asked to respond to an index of psychological stress symptoms (General Health Questionnaire GHQ-20). Those with high stress symptoms (GHQ ≥5) received home nursing visits. Control group patients received usual care. The sample consisted of 461 men, aged 31 to 86 years, who responded to the GHQ-20 before hospital discharge. Patients were followed for 5 years using record data. There were 321 Q-wave AMIs, 112 non-Q-wave AMIs and 28 indeterminate electrocardiograms. Life-table analyses showed that among patients with non-Q-wave AMIs receiving usual care, high stress in the hospital (GHQ ≥5) was associated with a 1-year relative risk (RR) of cardiac mortality of 5.49 ± 1.39 (p = 0.01). In comparison, control patients with Q-wave MIs had no stress-related increase in risk (RR = 0.41 ± 2.08, p = 0.40). In the treatment group, the patients with non-Q-wave AMIs did not experience an increase in risk associated with high stress (RR = 1.80 ± 1.79, p = 0.52). Further, this pattern of results was not altered by adjustment for covariates including previous history of AMI. In conclusion, the link between psychological stress and cardiac events is more apparent among patients with non-Q-wave than Q-wave AMI, and therefore stress-relieving interventions may be of particular value after non-Q-wave AMI.

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Recent studies have suggested a link between psychological status following an acute myocardial infarction (AMI) and long-term prognosis.[1–3] For example, secondary analyses of data from the 461 men involved in the Ischemic Heart Disease (IHD) Life Stress Monitoring Program,[2] a randomized clinical trial of a 1-year program of education and support following AMI, indicated that high levels of psychological symptoms of stress in the hospital have a long-term negative prognostic impact. Patients who had elevated scores on a measure of cognitive behavioral symptoms of psychological stress (the General Health Questionnaire GHQ-20[4]) and who received usual care had a more than two-fold increase in risk of cardiac mortality over 5 years (p = 0.018), and this risk remained even after control for other cardiac risk factors. Further, patients who took part in the treatment program did not experience a significant stress-related increase in long-term risk.

Perhaps the best documented model linking psychological status and cardiac outcome following AMI involves the combined impact of autonomic nervous system changes and myocardial ischemia on an infarct-damaged myocardium.[5–7] Thus, patients' vulnerability to psychological stress may be related to underlying ischemic risk. Work by Bissett et al,[8] as well as Gibson's team,[9] has shown that patients with non-Q-wave AMIs have greater areas of residual surviving tissue in the infarct-affected zone than do patients with Q-wave infarctions. In this context it seems reasonable to suggest that patients with non-Q-wave AMI might also be more vulnerable to the negative effects of psychological stress, and thus might benefit more from programs like the IHD Life Stress Monitoring Program. Thus, we hypothesized that, in the absence of supportive/educational interventions, non-Q-wave patients would be more susceptible to the negative impact of psychological stress than Q-wave patients.

METHODS

Treatment program: The details of the IHD Life Stress Monitoring Program have been described elsewhere.[10–12] In brief, the study involved a randomized, clinical trial of a 1-year program of monthly telephone monitoring of psychological stress symptoms coupled with home nursing visits for post-AMI patients reporting high levels of these symptoms during monthly monitoring calls. Patients in the treatment condition were telephoned at 1 week after discharge, and every month thereafter, and asked to respond to a standardized measure of psychological symptoms of stress, the GHQ-20.

TABLE I Frequency of Outcome Events at One and Five Years After AMI According to Treatment Group, AMI Type and Level of In-Hospital Stress*

	Control Patients				Treatment Patients			
	Non-Q-Wave (year)		Q-Wave (year)		Non-Q-Wave (year)		Q-Wave (year)	
	1	5	1	5	1	5	1	5
Total patients								
High stress	21		38		16		47	
Low stress	33		123		42		113	
Patients with known survival status								
High stress	21	21	37	31	16	13	46	41
Low stress	32	27	123	110	41	35	112	103
Cardiac mortality								
High stress	9 (42.9)	11 (52.4)	1 (2.7)	9 (29.0)	2 (12.5)	2 (15.4)	0 (0.0)	6 (14.6)
Low stress	3 (9.4)	5 (18.5)	8 (6.5)	19 (17.3)	3 (7.3)	5 (14.3)	6 (5.4)	22 (21.4)
Out-of-hospital mortality								
High stress	7 (33.3)	8 (38.1)	1 (2.7)	5 (4.1)	2 (12.5)	2 (15.4)	0 (0.0)	6 (14.6)
Low stress	1 (3.1)	2 (7.4)	5 (16.1)	14 (12.7)	2 (4.9)	3 (8.6)	2 (1.8)	10 (9.7)

*Numbers in parentheses represent the percentage of patients with known survival status who had each type of outcome.
AMI = acute myocardial infarction.

This index, originally designed to identify general practice patients most likely to benefit from psychiatric treatment, asks patients about the recent occurrence of 20 cognitive behavioral symptoms that people undergoing life stresses frequently report, such as difficulty sleeping, feelings of inadequacy and inability to concentrate. Because GHQ-20 scores tend to fluctuate in relation to difficulties in day-to-day adaptation to life circumstances, the scores are interpreted as a reflection of current levels of life stress rather than psychiatric illness per se.[2] Exploratory research using the GHQ-20 among post-AMI patients[13] led to the selection of a GHQ score of ≥5 of the 20 symptoms as the cutoff point for identifying high levels of psychological symptoms of stress. Thus, patients reporting ≥5 symptoms at any monitoring phone call were considered to be high stress patients in need of nursing interventions. Nursing interventions took place at patients' homes and involved combinations of support, education and referral which were individually tailored in terms of content, frequency and timing to the particular problems of each high stress patient. Interventions continued until a patient's monthly stress symptom score had decreased to below the cutoff point and the project team (consisting of a psychiatrist, a psychologist and project nurses) believed that no additional intervention was indicated. About half of the treatment group patients had monthly GHQ scores high enough to require nursing visits, and the average patient who received nursing interventions received 5 to 6 hours of nursing contact over 5 to 6 months.

Sample: Five hundred thirty-nine men recovering from a documented AMI in 3 McGill University teaching hospitals between November 1977 and May 1981 were randomly assigned to receive the treatment program or usual care. Informed consent was provided by 83% of those assigned to the treatment condition and 89% of those assigned to usual care. The final sample of 461 consenting patients ranged in age from 28 to 86 years (average 58). Seventy-five percent had not attended a university, and all but 18% were married or living with someone. Seventy percent had Q-wave AMIs, and 16% had experienced at least 1 previous infarction.

Data collection: Patients were interviewed in the hospital soon after discharge from coronary intensive care. Interviews included the GHQ-20 as well as a variety of questions concerned with medical history, behavioral risk factors for AMI, and demographic and psychosocial variables. Data on medical factors thought at the time of the original study to be important prognostic indicators[14] were obtained from hospital charts. Survival status at 1 and 5 years after the intake AMI was obtained from hospital records, Quebec Medicare data and death certificates. Details of the coding procedures for this data are provided in previous publications.[10,11] At the end of the trial, 1-year outcome data were available for 98% of the randomized sample (including the 27 treatment group patients who withdrew). Five-year outcome data were available for 88% of the original patients (Table I). In addition, to be able to assess the present hypothesis concerning the impact of psychological stress following non-Q-wave and Q-wave infarctions, the original data set was augmented with data on the type of AMI. Intake and discharge electrocardiograms were obtained from patients' hospital charts and blindly coded for the presence of Q waves using the modified Minnesota codes used in the Diltiazem Reinfarction Study.[15] Only 28 of the 461 patients (6.1%) had electrocardiograms which could not be coded for Q waves because of technical factors (e.g., pacemakers, left bundle branch block).

Data analysis: To test the hypothesis of interest, patients were divided into 8 subgroups based on the variables of in-hospital level of symptoms of psychological stress (high/low), AMI-type (non-Q/Q) and treatment group (treatment/control). Patients were classified as having high versus low levels of psychological stress

TABLE II One-Year Stress-Related Relative Risks* (with 95% confidence intervals) for Cardiac Mortality and Out-of-Hospital Mortality Among Control and Treatment Patients with Non-Q-Wave and Q-Wave AMI

Group	Relative Risk of Cardiac Mortality		Relative Risk of Out-of-Hospital Mortality	
	Raw	Adjusted†	Raw	Adjusted†
Non-Q-wave control patients	5.49 (±1.39) p = 0.011	4.24 (±1.33) p = 0.033	12.60 (±2.10) p = 0.018	9.41 (±2.13) p = 0.039
Q-wave control patients	0.41 (±2.08) p = 0.40	0.26 (±2.15) p = 0.22	0.65 (±2.15) p = 0.69	0.43 (±2.29) p = 0.47
Non-Q-wave treatment patients	1.80 (±1.79) p = 0.52	2.16 (±1.94) p = 0.44	2.70 (±1.96) p = 0.32	2.33 (±2.08) p = 0.42
Q-wave treatment patients	Not calculable‡		Not calculable§	

*Based on Cox proportional hazards regression analysis.
†See text for a description of covariates for which adjustment was made.
‡There were no cardiac deaths during the first year among high-stress Q-wave patients in the treatment group.
§There were no out-of-hospital deaths during the first year among high-stress Q-wave patients in the treatment group.
AMI = acute myocardial infarction.

TABLE III Five-Year Stress-Related Relative Risks* (with 95% confidence intervals) for Cardiac Mortality and Out-of-Hospital Mortality Among Control and Treatment Patients with Non-Q-Wave and Q-Wave AMI

Group	Relative Risk of Cardiac Mortality		Relative Risk of Out-of-Hospital Mortality	
	Raw	Adjusted†	Raw	Adjusted†
Non-Q-wave control patients	4.32 (±1.06) p = 0.0068	3.53 (±1.08) p = 0.022	7.66 (±1.55) p = 0.010	6.17 (±1.57) p = 0.023
Q-wave control patients	1.65 (±0.79) p = 0.21	1.45 (±0.86) p = 0.39	1.25 (±1.02) p = 0.67	1.47 (±1.05) p = 0.47
Non-Q-wave treatment patients	1.08 (±1.64) p = 0.93	1.22 (±1.85) p = 0.83	1.79 (±1.79) p = 0.52	1.84 (±1.92) p = 0.53
Q-wave treatment patients	0.63 (±0.90) p = 0.32	0.63 (±0.91) p = 0.33	1.40 (±1.01) p = 0.52	1.38 (±1.03) p = 0.54

*Based on Cox proportional hazards regression analysis.
†See text for a description of covariates for which adjustment was made.
AMI = acute myocardial infarction.

symptoms on the basis of their in-hospital GHQ scores. As in previous publications,[10,11] patients with in-hospital GHQ scores ≥5 were classified as having high stress and those with scores <5 were classified as having low stress. The number of patients in each cell whose survival status was known at the end of the first and fifth years is shown in Table I along with the actual number of outcome events.

Data analysis focused on the time from the index infarct to each of 2 outcomes (cardiac mortality, and out-of-hospital mortality, a proxy measure of sudden death) over 2 time intervals (the first year after infarct, and the 5-year follow-up period). For each outcome and time period the Kaplan-Meier survival curves for the 8 subgroups based on stress, AMI type and treatment group were compared using the generalized Mantel-Cox test (BMDP Program P1L[16]). For patients lost to follow-up, censoring took place on the last day on which the patient was known to be living. Significant interactions were further explored using a series of 2 by 2 survival curve comparisons to assess the hypothesized differences. The results of these analyses appear in Table II for the 1-year outcome data and in Table III for the outcomes over 5 years.

Because analysis in terms of the 3 major independent variables resulted in small sample sizes in some cells (Table I), we restricted our analyses for covariate control to 3 psychosocial variables (education, occupation, marital status) plus those cardiac variables in the data set shown in published reports to be the most important predictors following either non-Q-wave or Q-wave AMI, or to differentiate the 2 groups (age, previous AMI, congestive heart failure, ventricular arrhythmias, ST elevation at discharge, AMI recurrence in hospital, creatinine phosphokinase level, and prescription of β blockade at discharge).[17–22] Although diltiazem has been shown to have an impact on prognosis after non-Q-wave AMI,[15] this medication was not in common use at the time of the study, and no patient received it. In addition, although some patients were prescribed β blockers, and this variable has been included in the analyses, data collection took place before the results of the Beta-Blocker Heart Attack Trial were available,[22] and β blockers were not routinely prescribed. Whereas there is no evidence of any prognostic impact associated with the use of minor tranquilizers after an AMI, the present focus on the prognostic importance of psychological stress led us to include this

TABLE IV Significant* Independent Multivariate Predictors† of One- and Five-Year Cardiac Mortality and Out-of-Hospital Mortality Among Control and Treatment Patients with Non-Q-Wave and Q-Wave AMI

	1-Year		5-Year	
Group	Cardiac Mortality	Out-of-Hospital Mortality	Cardiac Mortality	Out-of-Hospital Mortality
Non-Q-wave control patients	Previous AMI	CHF	Previous AMI	Previous AMI
Q-wave control patients	Previous AMI	Age, β Blockade	Age, β Blockade, Previous AMI	Age, β Blockade
Non-Q-Wave treatment patients	0	0	CHF	0
Q-wave treatment patients	ST elevation at hospital discharge, minor tranquilizers	0	CHF	0

*$p \leq 0.05$ for all variables listed.
†Based on Cox proportional hazards regression analysis for combined high- and low-stress patients in each AMI-type/treatment group.
AMI = acute myocardial infarction; CHF = congestive heart failure.

variable. Complete data on all background variables of interest were available for 424 of the 431 subjects with codeable electrocardiograms (98.1% of non-Q-wave control, 96.4% of non-Q-wave treated, 97.5% of Q-wave control, 98.7% of Q-wave treated patients).

To select appropriate covariates for control in each 2 by 2 comparison, 2 steps were taken. First, to identify baseline differences in background characteristics that may have been responsible for any outcome differences observed between high- and low-stress patients, those with high and low stress in each AMI-type/treatment group were compared on all background variables using chi-square statistics for categoric variables (continuity corrections were applied for comparisons with expected frequencies of <5 in any cell) and independent *t* tests for continuous variables. All tests were 2-tailed. Second, to identify the significant ($p \leq 0.05$) multivariate predictors (other than stress) for each outcome in each AMI-type/treatment group, all covariates listed above (except for in-hospital stress) were entered into a separate Cox proportional hazards stepwise regression[23] for each outcome and each AMI-type/treatment group. Backwards elimination was used using the Peduzzi, Hardy and Holford method of computation (BMDP Program P2L).[16] The significant multivariate predictors of outcomes that emerged from these analyses are listed in Table IV. Finally, to assess the independent impact of in-hospital stress in each AMI-type/treatment group, all significant multivariate predictors for each outcome plus the significant baseline imbalances between high- and low-stress patients in each AMI-type/treatment group were first forced into a regression for each outcome followed by in-hospital stress. The covariate-adjusted relative risks associated with high levels of psychological stress are listed in Tables II and III.

RESULTS

The Mantel-Cox tests for all 8-group survival curve comparisons involving the interaction of in-hospital stress, type of AMI and treatment/control group were significant at $p < 0.001$. Therefore, the 2 by 2 comparisons described in the following sections were performed to examine high- and low-stress contrasts within each AMI-type/treatment group.

Impact of high stress in the non-Q-wave control group: The patients with non-Q-wave AMI who had high levels of psychological stress symptoms in the hospital and received usual care after discharge showed a marked increase in risk of cardiac mortality compared to patients with low in-hospital GHQ scores (Table II). High- and low-stress non-Q-wave patients in the control group did not differ significantly with regard to any of the baseline variables, and adjustment for the significant multivariate predictors in each cell (Table IV) did not alter the level of risk. Further, while the stress-related increase in risk was significant over the entire 5-year period, it was most marked during the first year after AMI (Figure 1).

Impact of high stress in the Q-wave control group: Among control patients with Q-wave infarcts there was little stress-related increase in risk over either the program year or the 5-year follow-up period (Table II and Figure 2). Within the Q-wave control group, patients with low levels of in-hospital stress were more likely to

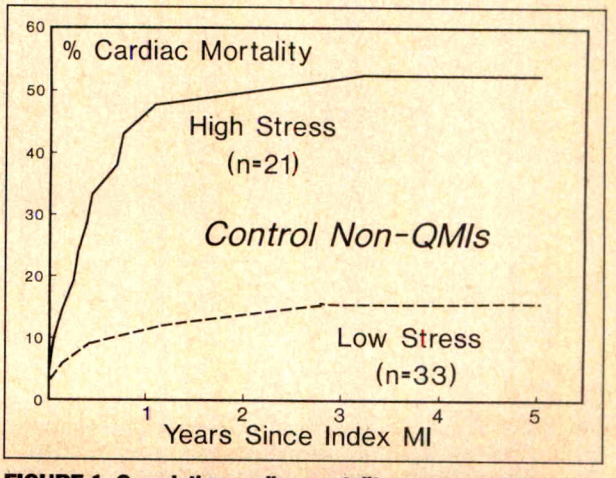


FIGURE 1. Cumulative cardiac mortality among control group patients with non-Q-wave myocardial infarctions (Non-QMIs) who had high (General Health Questionnaire score ≥5) and low (General Health Questionnaire <5) in-hospital stress.

be married than were patients with high stress. However, control for marital status and the significant multivariate predictors listed in Table IV did not change these results (Tables II and III).

It appears that, as hypothesized, with usual medical care, patients with non-Q-wave AMI are more susceptible to the impact of psychological stress than patients with Q-wave AMI. Further, whereas high-stress Q-wave patients do not experience an increase in risk over either the first year after AMI or the first 5 years after an infarct, the heightened risk associated with stress among non-Q-wave patients occurs primarily during the first year after AMI.

Impact of high stress in the non-Q-wave treatment group: Unlike the non-Q-wave patients who received routine medical care, those who took part in the treatment group experienced relatively little increase in risk associated with high levels of in-hospital stress (Figure 3 and Tables II and III). Background comparisons of the high- and low-stress non-Q-wave patients in the treatment group revealed that the high-stress treatment patients were significantly younger than the low-stress patients. However, control for age along with the significant multivariate predictors of outcome in this group (Table IV) did not decrease the probability levels associated with a stress-related difference in risk (Tables II and III). Thus, in contrast to the non-Q-wave control patients for whom high levels of in-hospital stress conferred a marked increase in risk, non-Q-wave treatment patients experienced little stress-related increase in risk.

Impact of high stress in the Q-wave treatment group: Patients with Q-wave AMI who took part in the treatment program also experienced little increase in stress-related risk (Tables II and III and Figure 4). In fact, none of the high-stress Q-wave patients in the treatment group died of cardiac causes during the program year. As in the non-Q-wave treatment group, patients with high-stress Q-wave AMI in the treatment group were older than patients with low stress, but control for this variable, along with the significant prognostic variables listed in Table IV, did not change the mortality pattern observed. Thus, regardless of whether or not they took part in the treatment program, high-stress Q-wave patients were at no greater mortality risk than low-stress patients. In contrast, with usual care, non-Q-wave patients who reported high levels of in-hospital stress were at markedly greater risk of cardiac death than patients with low stress, and those non-Q-wave patients who took part in the treatment program experienced no stress-related increase in risk.

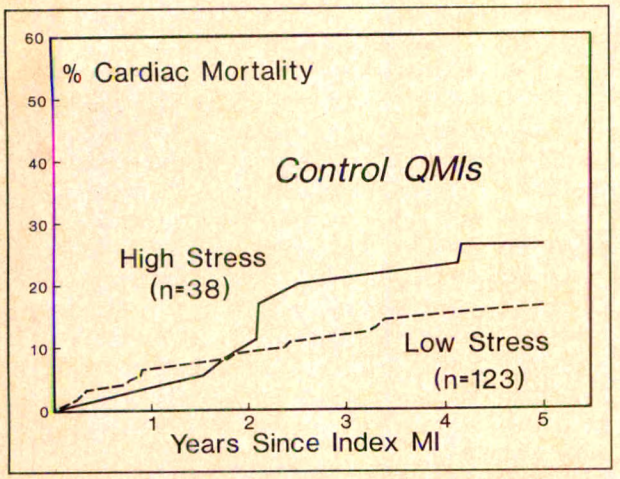


FIGURE 2. Cumulative cardiac mortality among control group patients with Q-wave myocardial infarctions (QMIs) who had high (General Health Questionnaire score ≥5) and low (General Health Questionnaire <5) in-hospital stress.

DISCUSSION

Although clearly a complex issue, the observed contrast between patients with Q-wave and non-Q-wave AMI in cardiac susceptibility to psychological stress could be explained in 2 ways, both of which are related to the greater infarct-related ischemic risk among non-Q-wave patients.[8,9] First, because of greater areas of re-

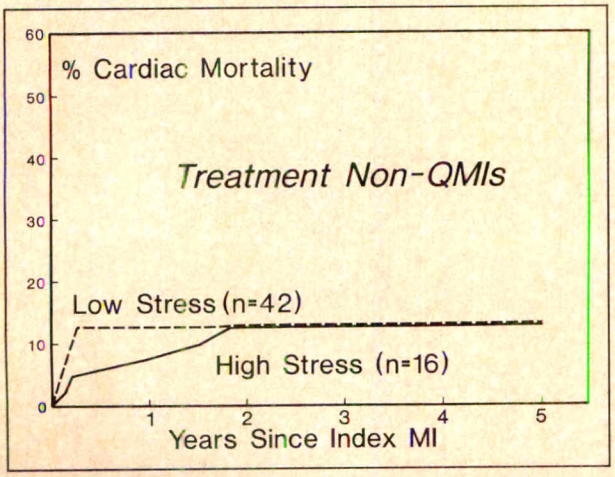


FIGURE 3. Cumulative cardiac mortality among treatment group patients with non-Q-wave myocardial infarctions (Non-QMIs) who had high (General Health Questionnaire score ≥5) and low (General Health Questionnaire <5) in-hospital stress.

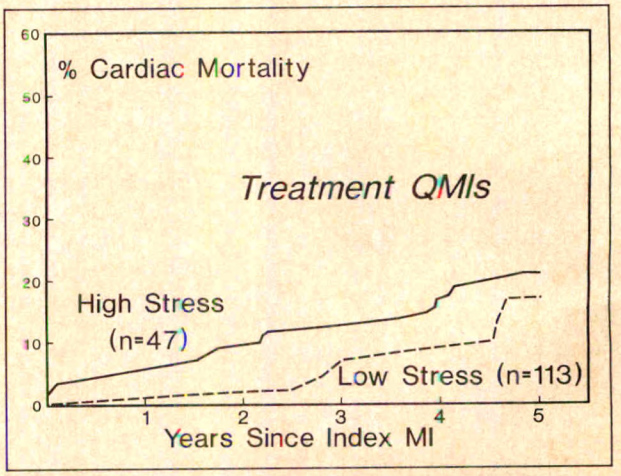


FIGURE 4. Cumulative cardiac mortality among treatment group patients with Q-wave myocardial infarctions (QMIs) who had high (General Health Questionnaire score ≥5) and low (General Health Questionnaire <5) in-hospital stress.

sidual myocardium at risk for ischemia, non-Q-wave patients may be more prone to fatal arrhythmias triggered by psychological stress. Animal experiments have shown that behavioral stress can induce sufficient changes in autonomic nervous system balance to decrease the electrical stability of the myocardium, and to have a profound effect on myocardial perfusion.[24] It is generally accepted that this combination of autonomic nervous system changes and myocardial ischemia plays a significant role in the genesis of fatal arrhythmias, particularly when the electrical properties of the myocardium have been altered by an infarction.[5] Recent laboratory work with humans has demonstrated that mental stress can provoke episodes of transient ischemia in patients with coronary artery disease,[25] affect the autonomic balance of the heart[26] and potentially trigger fatal ventricular arrhythmias.[27] Because it has been observed that the area of residual myocardium at jeopardy for ischemia is greater following non-Q-wave than Q-wave AMIs, the present finding that patients with non-Q-wave AMI are at greater risk of psychological stress than patients with Q-wave AMI fits this model well. The second explanation concerns the possibility that acute thrombus formation facilitated by stress-related changes in platelet aggregability or coronary vasospasm in the infarct-related vessel, or both, may be more likely to result in cardiac death after non-Q-wave infarction because of the larger area of residual ischemic tissue. Platelets have catecholamine-responsive α-receptor sites, theoretically making them susceptible to psychological stress.[28] Recent laboratory investigations performed by Grigani et al[29] indicate that there may be rapid changes in platelet aggregability following mental stress. Such changes may be particularly dangerous when the area of residual myocardium at risk for ischemia is large as in non-Q-wave AMIs. Our results indicate that with usual care, non-Q-wave patients with high levels of psychological stress in the hospital constitute a very high-risk group. Thus, interventions to lower stress would seem to be indicated for non-Q-wave patients reporting high stress. The need for this type of approach among Q-wave patients is not so clear. In fact, results among patients who participated in our 1-year program of monthly stress monitoring and nursing intervention showed that with intervention, non-Q-wave patients did not experience a stress-related increase in risk of cardiac death. Similarly, as occurred among the usual-care Q-wave patients, high-stress Q-wave patients who received treatment were at no greater risk of death than low-stress patients. Thus, while treatment impact was marked among high-stress non-Q-wave AMI patients, it was not apparent for either high- or low-stress Q-wave patients, or for those non-Q-wave patients who experienced low levels of in-hospital stress. Before suggesting that stress-relieving interventions may be of little value for these patients, it is important to consider study limitations. In addition to the methodologic limits of the original study,[10–12] the present analyses were not planned at the time of study design. Because of the number of comparisons involved in secondary analyses of this type, significant differences may be chance phenomena.[30] A second difficulty related to the post-hoc nature of the analyses is that sample sizes for some of the subgroups are smaller than needed to assure adequate statistical power to demonstrate a lack of differences between compared cells. Finally, data collection for this study took place between 1977 and 1981, before angioplasty and bypass surgery were frequently used to treat patients with non-Q-wave AMI with signs of residual ischemia. In addition, none of the patients with non-Q-wave infarction in the sample were given calcium antagonists.

In conclusion, it is possible that because of their unstable pathophysiology, the link between psychological and cardiac events is more apparent among patients with non-Q-wave infarcts than among those with Q-wave AMIs. Consequently, stress-relieving interventions may be of special benefit after non-Q-wave infarcts. Additional research is clearly warranted to establish the validity of these comparisons, and to further clarify the mechanisms linking psychological status and prognosis after AMI.

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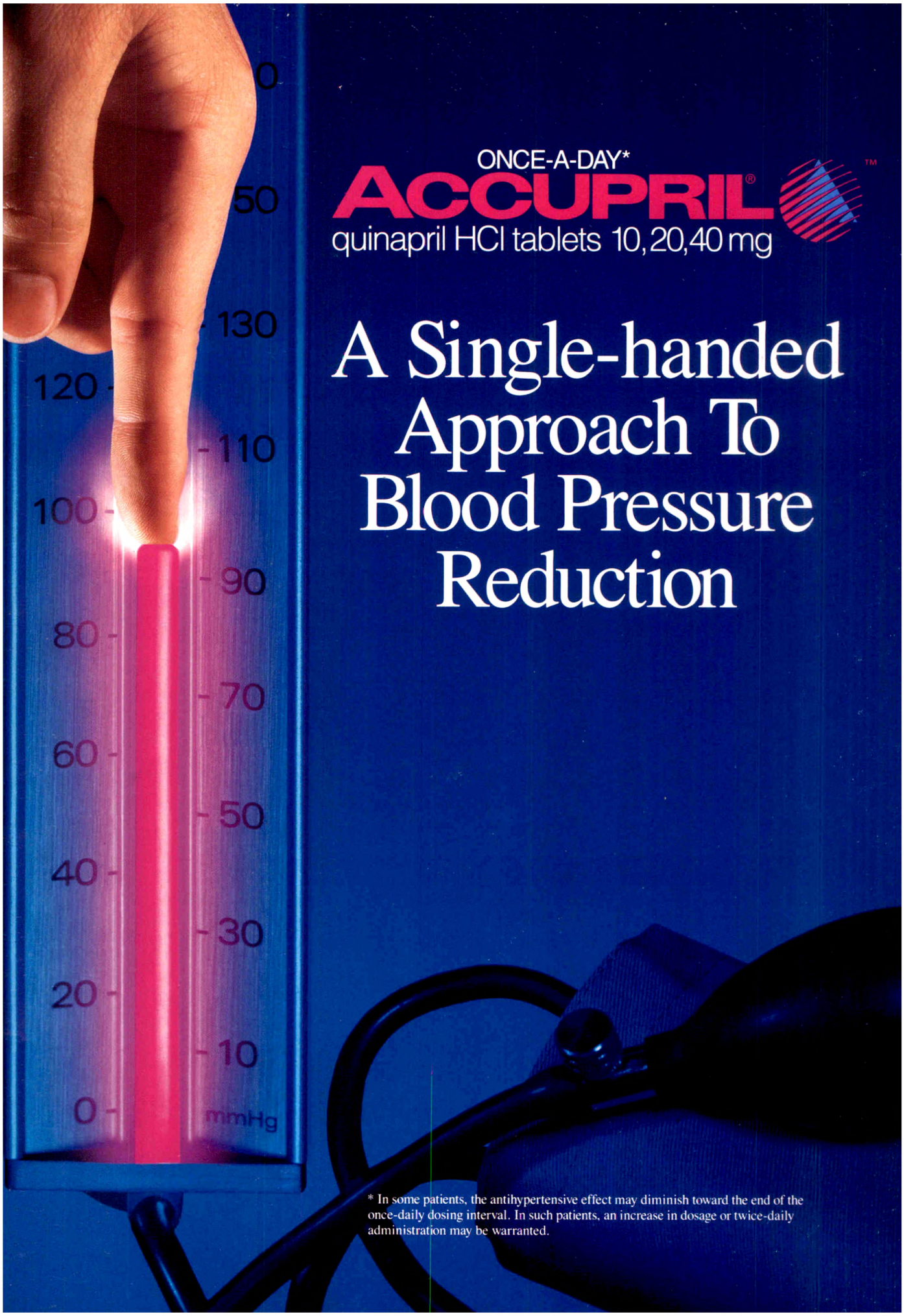
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INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

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Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effe

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diure the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase se potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concom tant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of se lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administere concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 tim the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m^2 basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames b terial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice *vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum d human dose when based on mg/kg and mg/m^2, respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, howeve milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma co centration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients; this appeared relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patie participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolle trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rare events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function test*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryng edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCU PRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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Prognosis of Acute Myocardial Infarction Complicated by Complete Heart Block (the Worcester Heart Attack Study)

Robert J. Goldberg, PhD, Juan C. Zevallos, MD, Jorge Yarzebski, MD, Joseph S. Alpert, MD, Joel M. Gore, MD, Zuoyao Chen, MD, MPH, and James E. Dalen, MD

As part of a community-based study of patients hospitalized with acute myocardial infarction (AMI) in the Worcester, Massachusetts, metropolitan area, changes over time in the incidence rates of complete heart block (CHB) complicating AMI, and the prognostic impact of CHB on the in-hospital and long-term survival of these patients were examined. In all, 4,762 patients with validated AMI hospitalized at 16 hospitals in the Worcester metropolitan area during 1975, 1978, 1981, 1984, 1986 and 1988 constituted the study sample. The incidence rates of CHB complicating AMI remained relatively stable at 5.8% over the 13-year (1975 to 1988) period studied. The incidence rates of CHB were approximately twice as high in patients with inferior/posterior wall AMI (7.7%) as in those with anterior wall AMI (3.9%). Use of a multivariate regression analysis to control for factors affecting the incidence rates of CHB revealed that patients were at highest risk for developing CHB during the latter 2 study years (1986 and 1988). Patients with AMI developing CHB had higher in-hospital case fatality rates than did those without CHB overall, as well as during each of the 6 periods studied. The in-hospital survival associated with CHB did not improve over time. After use of a multivariate regression analysis to control for additional prognostic factors, the independent effect of CHB on in-hospital prognosis remained (adjusted risk of dying = 2.10; 95% confidence intervals = 1.37, 3.21). Patients with inferior wall AMI complicated by CHB were at significantly increased risk of dying during hospitalization compared with those without CHB (adjusted risk of dying = 2.71; 95% confidence intervals = 1.60, 4.59). Long-term survival rates for up to a 14-year follow-up period for discharged surviving patients were not significantly different for AMI patients with compared with those without CHB, with no significant differences in long-term survival observed concerning the location of the AMI.

The results of this observational, population-based study suggest that the incidence rates of CHB resulting from AMI have not changed over time and that CHB is associated with an unfavorable short- but not long-term prognosis.

(Am J Cardiol 1992;69:1135–1141)

Patients developing complete heart block (CHB) in the setting of acute myocardial infarction (AMI) consistently have a poorer in-hospital survival when compared with those not developing CHB.[1–8] Furthermore, the anatomic location of the atrioventricular block has prognostic importance; AMI patients developing CHB complicating anterior wall AMI have a poorer prognostic outlook than do those with CHB complicating inferior wall AMI.[5,6,9,10] Studies examining the long-term prognosis for discharged surviving patients of CHB suggest no significant differences in 1-[2] or 2-year[4] survival rates in those with inferior wall AMI with and without CHB. However, questions may be raised concerning the generalizability of prior findings, because most of these studies were performed in either single or referral hospital settings. In addition, the independence of the short-term prognostic impact of CHB needs to be examined after controlling for other covariates of prognostic importance. Given interest in the natural history of AMI, and in new therapeutic and mechanical interventional approaches to its management, it is important to examine temporal trends in the incidence and survival rates of CHB complicating AMI, particularly as it relates to the current thrombolytic era. The present population-based study examines changes over time (1975 to 1988) in the incidence rates of CHB complicating AMI overall and separately in patients with anterior or inferior/posterior wall AMI. We also examined the impact of and temporal trends in CHB on the in-hospital and long-term survival of patients with AMI overall and classified according to the location of the AMI. The present investigation used data from 4,762 patients hospitalized with validated AMI from multiple hospitals in a defined population setting.

METHODS

Patients hospitalized with a primary or secondary discharge diagnosis of AMI (9th Revision International Classification of Disease [ICD] Code 410) in 16 Worcester, Massachusetts, Standard Metropolitan Statistical Area (SMSA) hospitals during 1975, 1978, 1981, 1984, 1986 and 1988 constituted the study population. Furthermore, a random sampling of related diag-

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TABLE I Incidence Rates and Adjusted Relative Risks of Complete Heart Block Complicating Acute Myocardial Infarction (AMI): Worcester Heart Attack Study

	All Patients		Anterior AMI		Inferior/Posterior AMI	
Year	Incidence Rates (%)	Adjusted Relative Risk	Incidence Rates (%)	Adjusted Relative Risk	Incidence Rates (%)	Adjusted Relative Risk
1975	5.1	1.0*	3.6	1.0*	6.6	1.0*
1978	6.8	1.14† (0.70, 1.85)‡	4.9	1.11 (0.48, 2.55)	8.5	1.17 (0.64, 2.14)
1981	5.2	1.01 (0.61, 1.65)	3.5	0.62 (0.26, 1.49)	6.9	1.16 (0.63, 2.11)
1984	5.0	1.09 (0.63, 1.86)	3.5	0.96 (0.38, 2.40)	6.7	1.14 (0.59, 2.23)
1986	5.9	1.51 (0.86, 2.66)	3.7	0.72 (0.29, 1.74)	8.3	1.89 (0.94, 3.79)
1988	7.3	1.92 (1.09, 3.41)	4.6	0.94 (0.37, 2.34)	9.2	2.42 (1.20, 4.88)
Total	5.8		3.9		7.7	

*Referrent category.
†Risk for developing complete heart block relative to those patients hospitalized in 1975 after controlling for differences in baseline predictive characteristics.
‡95% confidence intervals.

nostic rubrics in which the diagnosis of AMI may have occurred (ICD codes 411 through 414) was performed during each of the 6 years under study. The medical records of all patients with a discharge diagnosis of AMI from these hospitals were individually reviewed and validated according to preestablished diagnostic criteria that were previously described in detail.[11–13] Patients who did not satisfy the predetermined diagnostic criteria of clinical history, serum enzyme level elevations or serial electrocardiographic changes, or a combination, as well as those residing outside of the Worcester SMSA, were excluded from further consideration. The various clinical complications of AMI were assessed on the basis of information available from the clinical charts.[14] CHB was defined according to standard clinical criteria that included the absence of atrioventricular conduction on at least one 12-lead electrocardiogram with the atrial rate greater than the ventricular rate. We did not collect information concerning the settings in which CHB was documented, nor the extent or type of monitoring equipment used to detect CHB. Owing to the method of data abstraction we were unable to determine the duration of CHB, because we did not distinguish high-grade atrioventricular block from sustained periods of CHB.

Data collection: The hospital records of patients with validated AMI were abstracted for demographic and clinical data, as well as for use of selected therapeutic interventions. Survival status after hospital discharge was ascertained through a review of records for additional hospitalizations and by a statewide search of death certificates for residents of the Worcester SMSA. All-cause mortality was examined in relation to CHB among discharged surviving patients.

Statistical analysis: Differences in the distribution of selected characteristics between patients hospitalized for AMI with and without CHB were examined with the use of chi-square tests of statistical significance for discrete variables, and *t* tests for continuous variables. All tests of significance were 2-tailed. The short-term prognosis in each period was examined by calculating in-hospital case fatality rates (CFRs). The simultaneous effect of several potentially confounding variables that may influence the development of CHB, as well as in-hospital survival and changes therein, was accounted for by means of a logistic multiple regression technique.[15] The variables adjusted for in these analyses included time period, patient age and sex, order (initial vs recurrent), type (Q-wave vs non-Q-wave) and location (anterior vs inferior/posterior) of AMI, peak serum creatine kinase findings, occurrence of atrial fibrillation, congestive heart failure, cardiogenic shock and ventricular fibrillation/cardiac arrest during hospitalization, and use of β blockers, calcium antagonists, diuretics, lidocaine, other antiarrhythmic agents, nitrates and thrombolytic therapy, as well as cardiac pacing. A life table approach was used to examine long-term survival to include patients followed up for various lengths of time after hospital discharge.[16] Of the patients with validated AMI studied, 780 were hospitalized in 1975, 845 in 1978, 999 in 1981, 714 in 1984, 765 in 1986, and 659 in 1988.

RESULTS

Incidence rates of complete heart block: The incidence rates of CHB complicating AMI remained relatively stable over time (ranging from 5% in 1984 to 7.3% in 1988); the overall incidence rate of CHB was 5.8% (Table I). Because previous studies examined differences in the impact of CHB according to AMI location, we examined the incidence rates of CHB separately in patients with anterior and inferior/posterior wall AMI. Patients with inferior/posterior AMI were approximately twice as likely (7.7 vs 3.9%) to develop this conduction disturbance as were those with anterior AMI for the entire study period. Trends for an increased risk of developing CHB in patients with inferior/posterior wall AMI were seen in each of the 6 study periods examined (Table I). Because changes may have occurred in the demographic, clinical and therapeutic characteristics of patients hospitalized with

AMI over time, a logistic regression analysis was performed to examine changes over time in the occurrence rates of CHB while adjusting for these characteristics. The results of this multivariate analysis confirmed the univariate unadjusted findings of a lack of significant change over time in the overall occurrence rates of CHB, although the highest adjusted risks for developing CHB were seen in the latter 2 study years of 1986 and 1988 (Table I). Similar nonsignificant trends in the incidence rates of CHB were seen in patients with anterior and inferior/posterior AMI after multivariate adjustment. Similar to the overall findings, patients with inferior/posterior wall AMI in the latter 2 study years (1986 and 1988) were at greatest adjusted risk for developing CHB, with inconsistent trends observed for those with anterior wall AMI, although trends for these patients were in contrast to those with inferior/posterior AMI.

Baseline characteristics: Patients developing CHB during hospitalization for AMI included a significantly greater proportion of those with Q-wave and inferior/posterior AMI, larger infarcts (as measured by peak serum creatine kinase levels) and those developing each of the clinical complications examined during the acute hospitalization ($p < 0.001$) (Table II). Significant differences were also seen in the use of various therapeutic interventions in AMI patients with and without CHB. Cardiac pacing (as expected) was used to a significantly greater degree in AMI patients with CHB.

Over the combined study periods, patients with CHB in the setting of anterior wall AMI included a significantly greater proportion of those with prior diabetes, Q-wave AMI, more extensive myocardial damage (based on peak serum creatine kinase findings), and those who developed congestive heart failure, cardiogenic shock and ventricular fibrillation or cardiac arrest (Table III) ($p < 0.005$). Differences were also seen in the use of various therapies in patients with anterior wall AMI further classified according to occurrence of CHB. In examining similar baseline characteristics in patients with CHB in the setting of inferior/posterior wall AMI, those with CHB included a significantly greater proportion with Q-wave and more extensive AMI (as measured by peak creatine kinase findings), and those developing specific clinical complications during the acute hospital phase ($p < 0.001$). Significant differences were also observed in the use of various therapeutic regimens and cardiac pacing among patients with inferior/posterior wall AMI with and without CHB.

In-hospital case fatality rates: AMI patients developing CHB had significantly higher in-hospital CFRs overall (48.9 vs 16.4%), as well as during each of the 6 time periods examined (Figure 1).

The development of CHB in the setting of anterior wall AMI was associated with a significantly poorer overall in-hospital survival (CHB [+] CFR = 63% and CHB [−] CFR = 18.8%), with similar trends of an impaired in-hospital survival seen in those with inferior/posterior AMI complicated by third-degree heart block (CHB [+] CFR = 41.9%, and CHB [−] CFR = 14%; $p < 0.01$). As noted, patients developing CHB in the setting of anterior AMI (CFR = 63%) had a poorer in-hospital survival than did those with CHB and inferior/posterior AMI (CFR = 41.9%).

TABLE II Baseline Characteristics in Patients with Acute Myocardial Infarction (AMI) According to Complete Heart Block (CHB): Worcester Heart Attack Study

	CHB Present, % (n = 278)	CHB Absent, % (n = 4,484)	p Value
Characteristics			
Age (mean, yr)	68.3	66.8	NS
Men	59.4	61.5	NS
Prior history			
Angina	22.7	27.1	NS
Diabetes	28.1	22.9	NS
Hypertension	45.0	46.8	NS
AMI characteristics			
Initial AMI	68.7	65.9	NS
Q-Wave AMI	76.6	56.6	<0.001
Anterior AMI	33.1	50.0	<0.001
Peak CK ≥5× normal range	69.5	49.9	<0.001
Complications during hospitalization			
Atrial fibrillation	25.2	15.8	<0.001
Congestive heart failure	57.9	41.4	<0.001
Cardiogenic shock	23.4	6.5	<0.001
Ventricular fibrillation/cardiac arrest	54.2	17.8	<0.001
Therapies			
Anticoagulants	64.0	65.6	NS
Antiplatelets	19.8	22.2	NS
β blockers	29.5	40.5	<0.001
Calcium antagonists*	39.8	62.8	<0.001
Digoxin	42.1	36.8	NS
Diuretics	67.3	57.4	<0.005
Lidocaine	63.3	43.0	<0.001
Other antiarrhythmics	34.9	22.8	<0.001
Nitrates	74.5	80.5	<0.025
Pacing	61.2	5.8	<0.001
Thrombolytic agents*	9.7	14.7	NS

*Data available for 1986 and 1988 only.
CK = creatine kinase; NS = not significant.

Because AMI patients with compared with those without CHB differed with regard to various baseline characteristics (Table II), a logistic multiple regression approach was used to control simultaneously for these potentially confounding factors in examining the independence of the association of CHB to in-hospital survival. The results of this analysis yielded an adjusted risk of dying for AMI patients with CHB of 2.10 (95% confidence intervals [CI] = 1.37, 3.21). In a similar fashion, separate logistic regression analyses were performed to examine the prognostic impact of CHB according to AMI location while adjusting for similar potentially confounding prognostic factors. Among patients with anterior wall AMI, those developing CHB had a nonsignificant but increased risk of dying during the acute hospital phase of AMI compared with that of those without CHB (adjusted RR = 1.51; 95% CI = 0.74, 3.07); however, patients developing CHB in the setting of inferior/posterior wall AMI had a significantly increased risk of dying during this phase compared with that of those not developing CHB (adjusted RR = 2.71; 95% CI = 1.60, 4.59). A multivariate regression analysis was also performed to examine

TABLE III Baseline Characteristics in Patients with Acute Myocardial Infarction (AMI) According to Complete Heart Block (CHB) and AMI Location: Worcester Heart Attack Study

	Anterior AMI		Inferior/Posterior AMI	
	CHB Present, % (n = 92)	CHB Absent, % (n = 2,243)	CHB Present, % (n = 186)	CHB Absent, % (n = 2,241)
Characteristic				
Age (mean, yr)	70.7	67.7	67.1	65.9
Men	52.2	58.5	62.9	64.6
Prior history				
Angina	32.6	28.7	17.7	25.5
Diabetes	40.2	23.6	22.0	22.1
Hypertension	45.7	47.7	44.6	46.0
AMI characteristics				
Initial AMI	64.1	63.0	71.0	68.9
Q-wave AMI	71.7	52.5	79.0	60.7
Peak CK ≥ 5× normal range	65.6	47.1	71.4	52.7
Complications during hospitalization				
Atrial fibrillation	25.0	17.3	25.3	14.3
Congestive heart failure	73.9	46.8	50.0	36.0
Cardiogenic shock	31.5	6.8	19.4	6.3
Ventricular fibrillation/ cardiac arrest	71.9	19.5	45.7	16.1
Therapies				
Anticoagulants	59.8	65.4	66.1	65.8
Antiplatelets	18.5	20.8	20.4	23.6
β blockers	28.3	40.4	30.1	40.6
Calcium antagonists*	39.3	61.3	40.0	64.3
Digoxin	59.8	41.7	33.3	31.9
Diuretics	73.9	61.4	64.0	53.3
Lidocaine	66.3	42.9	61.8	43.2
Other antiarrhythmics	40.2	24.3	32.3	21.3
Nitrates	76.1	80.3	73.7	80.6
Pacing	63.0	5.4	60.2	6.3
Thrombolytic therapy*	3.6	14.5	12.3	14.9

*Data available for 1986 and 1988 only.
CK = creatine kinase.

changes over time (1975 to 1988) in the in-hospital survival of AMI patients with CHB, while controlling for the previously mentioned prognostic characteristics. The results of this analysis did not demonstrate improvement over time in the short-term prognosis of patients with CHB after adjusting for these factors.

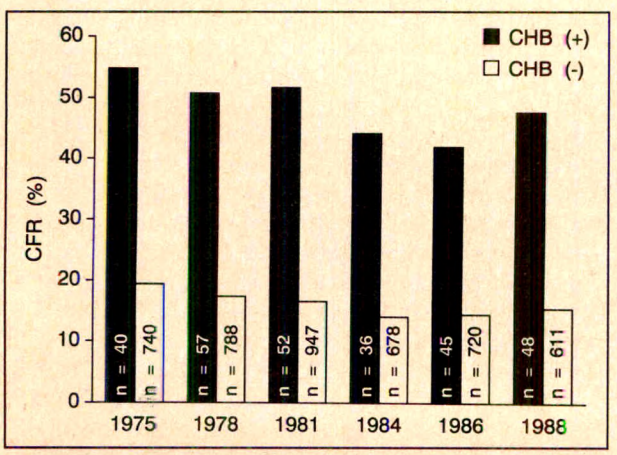


FIGURE 1. In-hospital case fatality rates (CFR) of acute myocardial infarction according to occurrence of complete heart block (CHB) and time period: Worcester Heart Attack Study.

Long-term survival: The long-term survival for the 142 AMI patients whose acute hospitalization was complicated by CHB was not significantly different from that for the 3,748 without CHB (Figure 2). In examining the long-term prognostic impact of CHB according to AMI location, there were no significant differences in long-term survival for patients with and without CHB in the setting of either anterior or inferior/posterior wall AMI (Figure 3). However, a particularly adverse impact of CHB on the 5-year survival rate for patients with anterior AMI was observed.

DISCUSSION

The results of this community-wide study performed in multiple hospitals in the Worcester SMSA show relative constancy in the occurrence rates of CHB complicating AMI over the periods under study (1975 to 1988), a consistently greater incidence of CHB in patients with inferior/posterior than anterior wall AMI, a significant adverse impact of CHB on in-hospital survival (particularly among those with inferior/posterior AMI), with a lack of improvement over time in the in-hospital survival of those with CHB, and a lack of impact of this conduction disturbance on the long-term prognosis of discharged hospital patients.

Incidence rates of complete heart block: Previous studies examining the incidence rates of CHB resulting from AMI reported incidence rates as low as several percent to almost 20%.[1-4,17-20] In reviewing studies examining the incidence rates of CHB in inferior wall AMI, on average, approximately 12% of the patients included in these studies developed third-degree heart block (range 8 to 18%).[17] Factors associated with an increased likelihood of CHB included diabetes mellitus,[21] use of continuous electrocardiographic monitoring,[19,22] concomitant adverse prognostic characteristics, and larger and more extensive AMIs.[1-3,7,23,24]

The results of the present study are consistent with findings from previous investigations that showed all forms of CHB to occur more frequently in the setting of acute inferior rather than anterior wall AMI.[5,6,9,25] This increased incidence of advanced heart block in the setting of inferior AMI is thought to be the result of block above the His bundle, based on electrophysiologic studies.[26-28] In contrast, development of CHB in patients with anterior wall AMI is thought to occur secondary to infra-Hisian atrioventricular block, with the majority of these presenting with bundle branch block before the development of CHB.[26,27]

The absence of significant change over time in both the crude as well as adjusted incidence rates of CHB overall, as well as according to AMI location, during the periods studied (1975 to 1988) was of interest. However, it should be noted that for all AMI patients studied, and particularly for those with inferior wall AMI, the highest observed multivariate adjusted risks for CHB were seen during the most recent study years (1986 and 1988). This is particularly relevant because a decrease in the incidence rates of CHB may have been

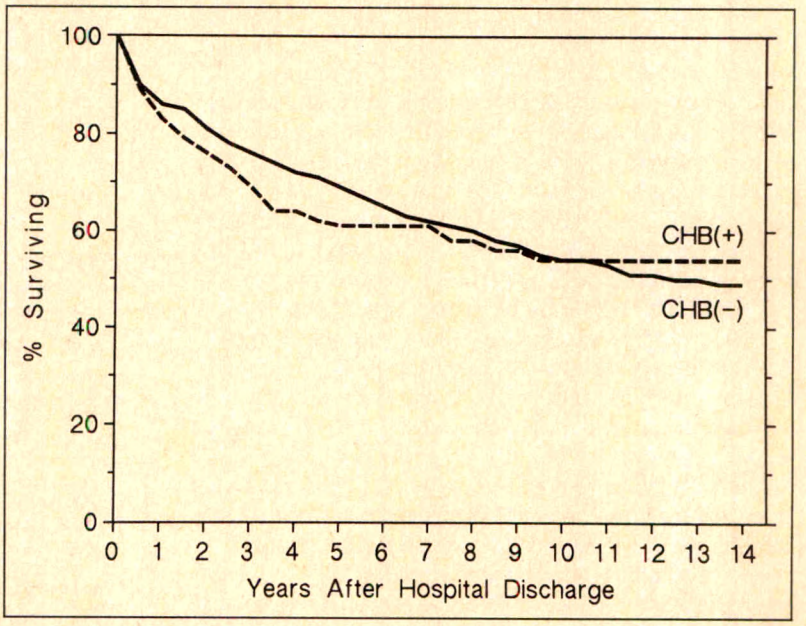


FIGURE 2. Long-term survival after acute myocardial infarction according to occurrence of complete heart block (CHB): Worcester Heart Attack Study.

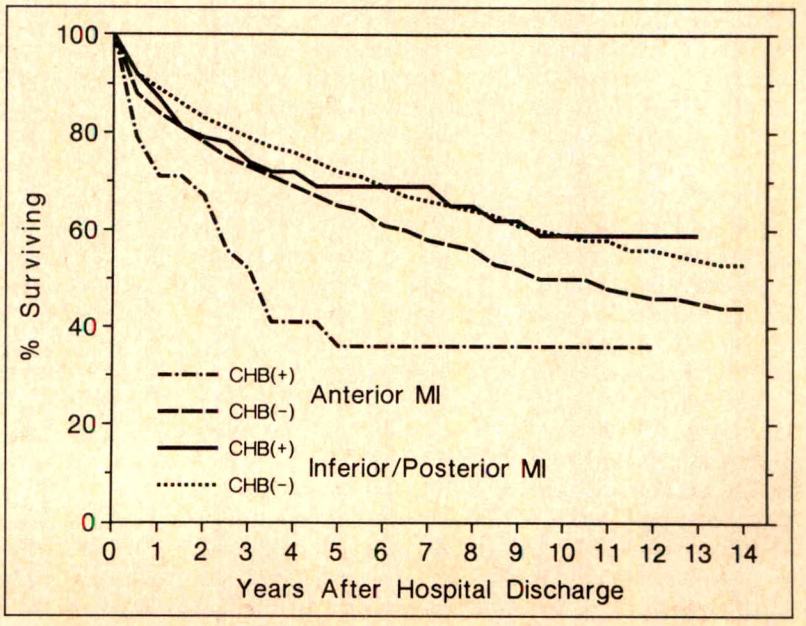


FIGURE 3. Long-term survival after acute myocardial infarction (MI) according to occurrence of complete heart block (CHB) and to location of infarction: Worcester Heart Attack Study.

expected during the most recent time periods in which newer interventions and therapies to limit infarct size and enhance coronary perfusion were introduced. However, as previously noted, AMI patients developing CHB were less likely to have received calcium antagonists and thrombolytic agents than those not developing CHB, and whereas the overall use of thrombolytic agents in this study was low it was comparable to the rates of thrombolytic therapy in a recent community-based study performed in western Washington.[29] However, the higher incidence rates for CHB observed in 1986 and 1988 may be related to improved and more thorough monitoring of hospitalized AMI patients. The present findings are consistent with a recent investigation showing an incidence rate of CHB (13%) among patients with inferior AMI to be similar to that previously reported despite the use of thrombolytic therapy in the population studied.[4]

In-hospital survival: An approximately twofold increased risk of dying during hospitalization was observed for AMI patients with CHB after adjusting for additional factors of short-term prognostic significance. Whereas AMI patients with CHB fared worse in the short term, the adverse prognostic impact of CHB was observed (particularly among those with inferior/posterior AMI) after adjusting for a number of potentially confounding prognostic factors. In both crude and multivariate adjusted analyses, the in-hospital prognosis of patients with CHB did not improve over time.

Most studies examining the prognostic impact of CHB after AMI observed an increased death rate among these patients, with a marked differential in short-term survival for those with anterior compared with inferior wall AMI.[1–4,22] Patients developing CHB are thought to have a poorer in-hospital survival owing to either the simultaneous occurrence of accompanying left ventricular failure or to the conduction disturbance itself. As observed in the present study, AMI patients with CHB included a significantly greater proportion of those with more extensive acute myocardial damage. However, when these and additional factors were adjusted for, the independent effect of CHB on in-hospital mortality was upheld. Dual impairment of the atrioventricular nodal blood supply has been postulated to explain, in part, the greater likelihood of clinical complications accompanying AMI, and the poorer in-hospital survival for patients with CHB. The increased mortality rate in patients with anterior wall AMI is thought to be due to more extensive myocardial necrosis and greater left ventricular dysfunction. Patients developing CHB in the setting of inferior wall AMI are thought to have an increased short-term mortality due to more extensive underlying coronary artery disease or greater occurrence of left ventricular failure, or both.[1,7,9,17,27] The independent effect of CHB on in-hospital mortality among patients with inferior wall AMI was confirmed in 2 recent studies[2,4] that also adjusted for concomitant short-term prognostic factors. The absence of improvement over time in the short-term survival of patients with CHB reinforces the need for the systematic evaluation and identification of therapies designed to reduce not only the incidence rates of CHB complicating AMI, but also to improve its in-hospital survival.

Long-term survival: Limited data exist concerning the impact of CHB on the long-term prognosis of discharged AMI patients.[2,4] Two recent studies showed no significant difference in long-term survival according to the presence of CHB during hospitalization for acute inferior AMI.[2,4] These findings together with the results of the present investigation suggest that the mortality for patients discharged from the hospital after CHB resulting from AMI is similar to that for those who do not develop CHB. Despite the fact that the long-term survival curves were not significantly different, the lower observed survival rate (particularly within the first several years after hospital discharge) among patients with anterior AMI and CHB needs further investigation.

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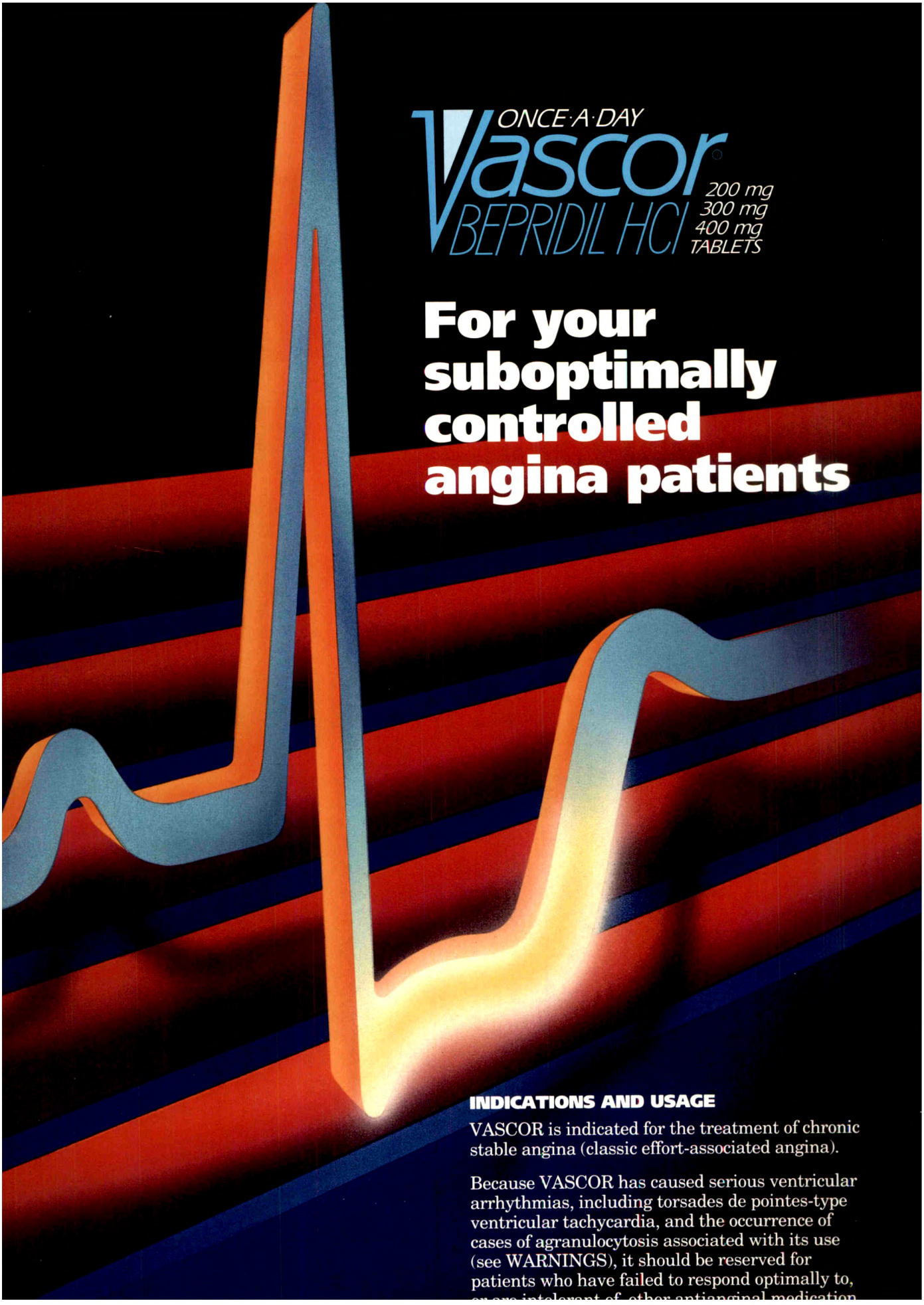
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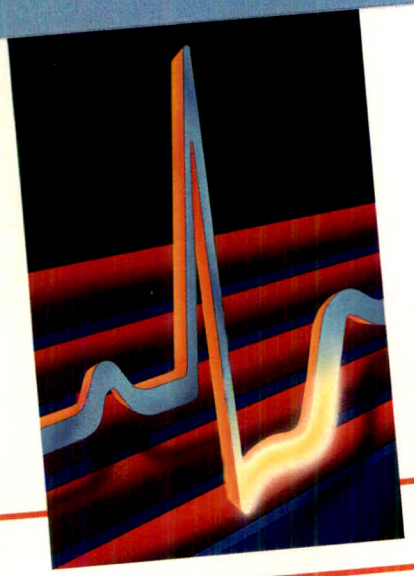
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Because VASCOR has caused serious ventricular arrhythmias, including torsades de pointes-type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to,



Another in a series of actual case reports

A CASE FOR VASCOR® (bepridil HCl)

James P., 58-year-old building painter*

PRESENTING SYMPTOM: Could not continue to work because of limiting angina

HISTORY: Suboptimal response to a regimen of atenolol, diltiazem, and isosorbide dinitrate; remains uncontrolled despite angioplasty

EXERCISE TOLERANCE TEST:
Total exercise time: 5 min, 1 sec
Time to 1-mm ST depression: 3 min, 12 sec
Time to onset of angina: 2 min, 52 sec

LABORATORY FINDINGS:
Serum potassium: 4.3 mEq/L
ECG: Nonspecific ST abnormality
QTc interval: 406 msec

CLINICAL COURSE: Diltiazem discontinued; VASCOR 200 mg QD initiated, resulting in some improvement after 2 weeks; VASCOR dosage increased to 300 mg QD, resulting in marked improvement after 4 weeks

EXERCISE TOLERANCE TEST:
Total exercise time: 6 min, 1 sec
Time to 1-mm ST depression: 4 min, 12 sec
Time to onset of angina: 4 min, 2 sec
QTc interval range: 440 to 460 msec

FOLLOW-UP: **Over the next 3 months, James P. was able to return to his job part-time and experienced angina only with extreme exertion**

ONCE·A·DAY
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Tablets For Oral Administration

Brief Summary

INDICATIONS AND USAGE
Chronic Stable Angina (Classic Effort-Associated Angina)

VASCOR (bepridil hydrochloride) is indicated for the treatment of chronic stable angina (classic effort-associated angina). Because VASCOR has caused serious ventricular arrhythmias, including torsades de pointes type ventricular tachycardia, and the occurrence of cases of agranulocytosis associated with its use (see WARNINGS), it should be reserved for patients who have failed to respond optimally to, or are intolerant of, other anti-anginal medication.

VASCOR may be used alone or in combination with beta blockers and/or nitrates. Controlled clinical studies have shown an added effect when VASCOR is administered to patients already receiving propranolol.

CONTRAINDICATIONS
VASCOR (bepridil hydrochloride) is contraindicated in patients with a known sensitivity to bepridil hydrochloride.

VASCOR is contraindicated in (1) patients with a history of serious ventricular arrhythmias (see WARNINGS–Induction of New Serious Arrhythmias), (2) patients with sick sinus syndrome or patients with second- or third-degree AV block, except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients with uncompensated cardiac insufficiency, (5) patients with congenital QT interval prolongation (see WARNINGS), and (6) patients taking other drugs that prolong QT interval (see PRECAUTIONS-Drug Interactions).

WARNINGS
Induction of New Serious Arrhythmias

VASCOR (bepridil hydrochloride) has Class 1 anti-arrhythmic properties and, like other such drugs, can induce new arrhythmias, including VT/VF. In addition, because of its ability to prolong the QT interval, VASCOR can cause torsades de pointes type ventricular tachycardia. Because of these properties VASCOR should be reserved for patients in whom other anti-anginal agents do not offer a satisfactory effect.

In US clinical trials, the QT and QTc intervals were commonly prolonged by VASCOR in a dose-related fashion. While the mean prolongation of QTc was 8% and of QT was 10%, QTc increases of 25% or more were not uncommon, 5%; 8.7% QT. Increased QT and QTc may be associated with torsades de pointes type VT, which was seen at least briefly, in about 1.0% of patients in US trials; in many cases, however, patients with marked prolongation of QTc were taken off VASCOR therapy. All of the US patients with torsades de pointes had a prolonged QT interval and relatively low serum potassium. French marketing experience has reported over one hundred verified cases of torsades de pointes. While this number, based on total use, represents a rate of only 0.01%, the true rate is undoubtedly much higher, as spontaneous reporting systems all suffer from substantial under reporting.

Torsades de pointes is a polymorphic ventricular tachycardia often but not always associated with a prolonged QT interval, and often drug induced. The relation between the degree of QT prolongation and the development of torsades de pointes is not linear and the likelihood of torsades appears to be increased by hypokalemia, use of potassium wasting diuretics, and the presence of antecedent bradycardia. While the safe upper limit of QT is not defined, it is suggested that the interval not be permitted to exceed 0.52 seconds during treatment. If dose reduction does not eliminate the excessive prolongation, VASCOR should be stopped.

Because most domestic and foreign cases of torsades have developed in patients with hypokalemia, usually related to diuretic use or significant liver disease, if concomitant diuretics are needed, low doses and addition or primary use of a potassium sparing diuretic should be considered and serum potassium should be monitored.

VASCOR has been associated with the usual range of pro-arrhythmic effects characteristic of Class 1 anti-arrhythmics (increased premature ventricular contraction rates, new sustained VT, and VT/VF that is more difficult than previously to convert to sinus rhythm). Use in patients with severe arrhythmias (who are most susceptible to certain pro-arrhythmic effects) has been limited, so that risk in these patients is not defined.

In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-centered, randomized, double-blind study in patients with asymptomatic nonlife-threatening ventricular arrhythmias who had myocardial infarctions more than six days but less than two years previously, an excess mortality/non-fatal cardiac arrest rate was seen in patients treated with encainide or flecainide (56/730) compared with that seen in patients assigned to matched placebo-treated groups (22/725). The applicability of these results to other populations (e.g., those without recent myocardial infarction) or to other anti-arrhythmic drugs is uncertain, but at present it is prudent to consider any drug documented to provoke new serious arrhythmias or worsening of preexisting arrhythmias as having a similar risk and to avoid their use in the post-infarction period.

Agranulocytosis: In US clinical trials of over 800 patients treated with VASCOR for up to five years, two cases of marked leukopenia and neutropenia were reported. Both patients were diabetic and elderly. One died with overwhelming gram-negative sepsis, itself a possible cause of marked leukopenia. The other patient recovered rapidly when VASCOR was stopped.

Congestive Heart Failure: Congestive heart failure has been observed infrequently (about 1%) during US controlled clinical trials, but experience with the use of VASCOR in patients with significantly impaired ventricular function is limited. There is little information on the effect of concomitant administration of VASCOR and digoxin; therefore, caution should be exercised in treating patients with congestive heart failure.

Hepatic Enzyme Elevation: In US clinical studies with VASCOR in about 1000 patients and subjects, clinically significant (at least 2 times the upper limit of normal) transaminase elevations were observed in approximately 1% of the patients. None of these patients became clinically symptomatic or jaundiced and values returned to normal when the drug was stopped.

Hypokalemia: In clinical trials VASCOR has not been reported to reduce serum potassium levels. Because hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency should be corrected before VASCOR therapy is initiated and normal potassium concentrations should be maintained during VASCOR therapy. Serum potassium should be monitored periodically.

PRECAUTIONS
General

Caution should be exercised when using VASCOR (bepridil hydrochloride) in patients with left bundle branch block or sinus bradycardia (less than 50 b.p.m.). Care should also be exercised in patients with serious hepatic or renal disorders because such patients have not been studied and bepridil is highly metabolized, with metabolites excreted primarily in the urine.

Recent Myocardial Infarction

In US clinical trials with VASCOR, patients with myocardial infarctions within three months prior to initiation of drug treatment were excluded. The initiation of VASCOR therapy in such patients, therefore, cannot be recommended.

Information for Patients

Since QT prolongation is not associated with defined symptomatology, patients should be instructed on the importance of maintaining any potassium supplementation or potassium sparing diuretic, and the need for routine electrocardiograms and periodic monitoring of serum potassium.

The following Patient Information is printed on the carton label of each unit of use bottle of 30 tablets:

As with any medication that you take, you should notify your physician of any changes in your overall condition. Insure that you follow your physician's instructions regarding follow-up visits. Please notify any physician who treats you for a medical condition that you are taking VASCOR® (bepridil hydrochloride), as well as any other medications.

Drug Interactions

Nitrates: The concomitant use of VASCOR with long- and short-acting nitrates has been safely tolerated in patients with stable angina pectoris. Sublingual nitroglycerin may be taken if necessary for the control of acute angina attacks during VASCOR therapy.

Beta-blocking Agents: The concomitant use of VASCOR and beta-blocking agents has been well tolerated in patients with stable angina. Available data are not sufficient, however, to predict the effects of concomitant medication on patients with impaired ventricular function or cardiac conduction abnormalities (see DOSAGE AND ADMINISTRATION).

Digoxin: In controlled studies in healthy volunteers, bepridil hydrochloride either had no effect (one study) or was associated with modest increases, about 30% (two studies) in steady-state serum digoxin concentrations. Limited clinical data in angina patients receiving concomitant bepridil hydrochloride and digoxin therapy indicate no discernible changes in serum digoxin levels. Available data are neither sufficient to rule out possible increases in serum digoxin with concomitant treatment in some patients, nor other possible interactions, particularly in patients with cardiac conduction abnormalities (also see WARNINGS–Congestive Heart Failure).

Oral Hypoglycemics: VASCOR has been safely used in diabetic patients without significantly lowering their blood glucose levels or altering their need for insulin or oral hypoglycemic agents.

General Interactions: Certain drugs could increase the likelihood of potentially serious adverse effects with bepridil hydrochloride. In general, these are drugs that have one or more pharmacologic activities similar to bepridil hydrochloride, including anti-arrhythmic agents such as quinidine and procainamide, cardiac glycosides and tricyclic anti-depressants. Anti-arrhythmics and tricyclic anti-depressants could exaggerate the prolongation of the QT interval observed with bepridil hydrochloride. Cardiac glycosides could exaggerate the depression of AV nodal conduction observed with bepridil hydrochloride.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was revealed in one lifetime study in mice at dosages up to 60 times (for a 60 kg subject) the maximum recommended dosage in man. Unilateral follicular adenomas of the thyroid were observed in a study in rats following lifetime administration of high doses of bepridil hydrochloride, i.e., ≥ 100 mg/kg/day (20 times the usual recommended dose in man). No mutagenic or other genotoxic potential of bepridil hydrochloride was found in the following standard laboratory tests: the Micronucleus Test for Chromosomal Effects, the Liver Microsome Activated Bacterial Assay for Mutagenicity, the Chinese Hamster Ovary Cell Assay for Mutagenicity, and the Sister Chromatid Exchange Assay. No intrinsic effect on fertility by bepridil hydrochloride was demonstrated in rats.

In monkeys, at 200 mg/kg/day, there was a decrease in testicular weight and spermatogenesis. There were no systematic studies in man related to this point. In rats, at doses up to 300 mg/kg/day, there was no observed alteration of mating behavior nor of reproductive performance.

Usage in Pregnancy

Pregnancy Category C. Reproductive studies (fertility and peri-postnatal) have been conducted in rats. Reduced litter size at birth and decreased pup survival during lactation were observed at maternal dosages 37 times (on a mg/kg basis) the maximum daily recommended therapeutic dosage.

In teratology studies, no effects were observed in rats or rabbits at these same dosages.

There are no well-controlled studies in pregnant women. Use VASCOR in pregnant or nursing women only if the potential benefit justifies the potential risk.

Nursing Mothers

Bepridil is excreted in human milk. Bepridil concentration in human milk is estimated to reach about one third the concentration in serum. Because of the potential for serious adverse reactions in nursing infants from VASCOR a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of VASCOR in children have not been established.

ADVERSE REACTIONS
Adverse reactions were assessed in 529 patients who received VASCOR (bepridil hydrochloride) in controlled trials of 4-12 weeks duration and longer-term uncontrolled studies. The most common side effects occurring more frequently than in control groups were upper gastrointestinal complaints (nausea, dyspepsia or GI distress) in about 22%, diarrhea in about 8%, dizziness in about 15%, asthenia in about 10% and nervousness in about 7%. The adverse reactions seen in at least 2% of bepridil patients in controlled trials are shown in the following list.

Body as a Whole: Asthenia, Headache, Flu Syndrome **Cardiovascular/Respiratory:** Palpitations, Dyspnea, Respiratory Infection **Gastrointestinal:** Dyspepsia, G.I. Distress, Nausea, Dry Mouth, Anorexia, Diarrhea, Abdominal Pain, Constipation **Central Nervous System:** Drowsy, Insomnia, Dizziness, Tremor, Tremor of Hand, Paresthesia **Psychiatric:** Nervous **Special Senses:** Tinnitus.

About 15% of patients however, left bepridil treatment because of adverse experiences. In controlled clinical trials, these were principally gastrointestinal (1.0%), dizziness (1.0%), ventricular arrhythmias (1.0%) and syncope (0.6%).

Across all controlled and uncontrolled trials, VASCOR was evaluated in over 800 patients with chronic angina. In addition to the adverse reactions noted above, the following were observed in 0.5 to 2.0% of the VASCOR patients or are rarer, but potentially important events seen in clinical studies or reported in post marketing experience. In most cases it is not possible to determine whether there is a causal relationship to bepridil treatment.

Body as a Whole: Fever, pain, myalgic asthenia, superinfection, flu syndrome. **Cardiovascular/Respiratory:** Sinus tachycardia, sinus bradycardia, hypertension, vasodilation, edema, ventricular premature contractions, ventricular tachycardia, prolonged QT interval, rhinitis, cough, pharyngitis. **Gastrointestinal:** Flatulence, gastritis, appetite increase, dry mouth, constipation. **Musculoskeletal:** Arthritis. **Central Nervous System:** Fainting, vertigo, akathisia, drowsiness, insomnia, tremor. **Psychiatric:** Depression, anxiousness, adverse behavior effect. **Skin:** Rash, sweating, skin irritation. **Special Senses:** Blurred vision, tinnitus, taste change. **Urogenital:** Loss of libido, impotence. **Abnormal Lab Values:** Abnormal liver function test, SGPT increase.

Certain cardiovascular events, such as acute myocardial infarction (about 3% of patients) worsened heart failure (1.9%), worsened angina (4.5%), severe arrhythmia (about 2.4% VT/VF) and sudden death (1.6%) have occurred in patients receiving bepridil, but have not been included as adverse events because they appear to be, and cannot be distinguished from, manifestations of the patient's underlying cardiac disease. Such events as torsades de pointes arrhythmias, prolonged QT/QTc, bradycardia, first degree heart block, which are probably related to bepridil, are included in the tables.

OVERDOSAGE
In the event of overdosage, we recommend close observation in a cardiac care facility for a minimum of 48 hours and use of appropriate supportive measures in addition to gastric lavage. Beta-adrenergic stimulation or parenteral administration of calcium solutions may increase transmembrane calcium ion influx. Clinically significant hypotensive reactions or high-degree AV block should be treated with vasopressor agents or cardiac pacing, respectively. Ventricular tachycardia should be handled by cardioversion and, if persistent, by overdrive pacing. There has been one experience with overdosage in which a patient inadvertently took a single dose of 1600 mg of VASCOR (bepridil hydrochloride). The patient was observed for 72 hours in intensive care, but no significant adverse experiences were noted.

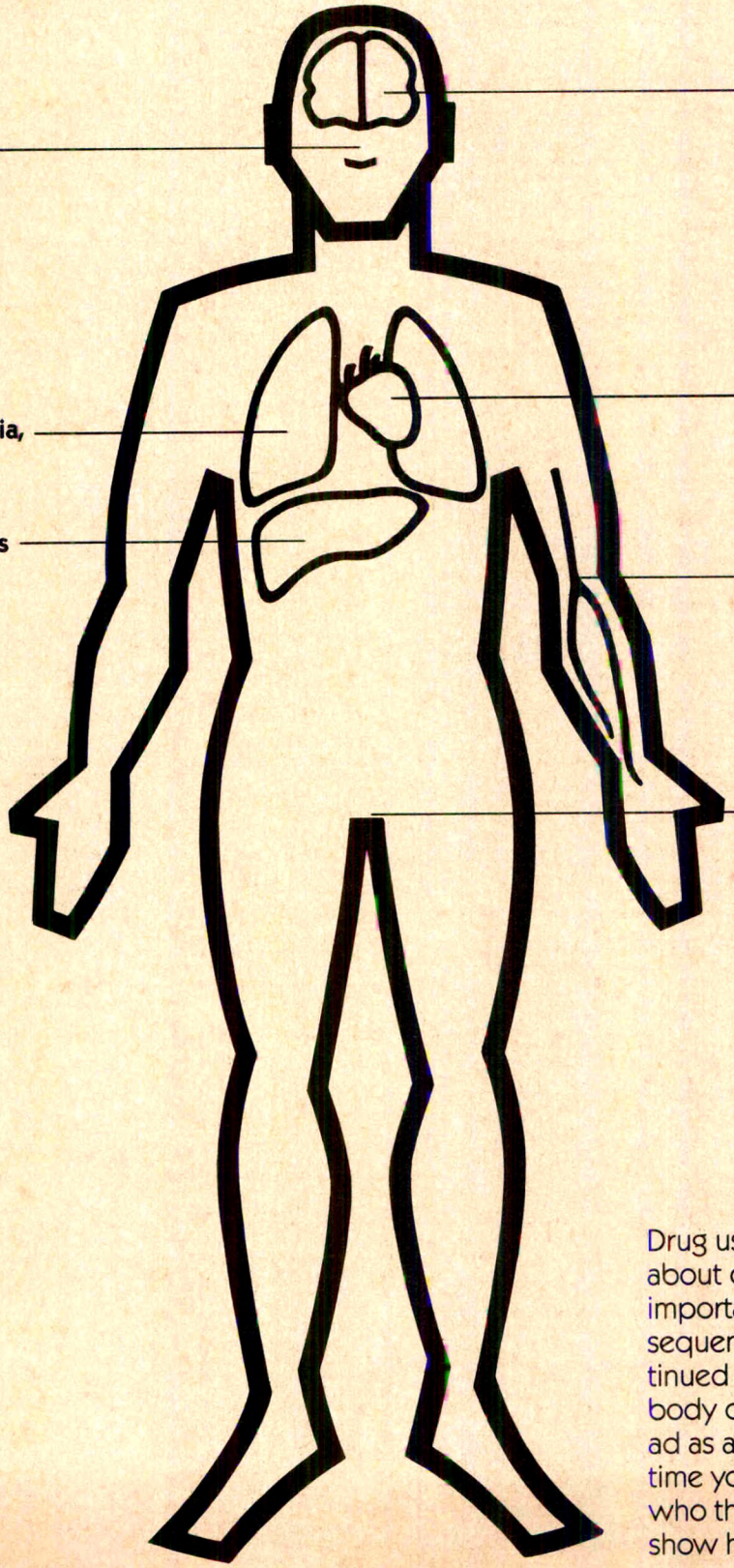
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Effect of Spinal Cord Stimulation on Regional Myocardial Perfusion Assessed by Positron Emission Tomography

Christian De Landsheere, MD, Clas Mannheimer, MD, PhD, Alfons Habets, PhD, Marcel Guillaume, PhD, Ivan Bourgeois, Lars-Erik Augustinsson, MD, Tore Eliasson, MD, Daniel Lamotte, Henri Kulbertus, MD, and Pierre Rigo, MD

Spinal cord stimulation (SCS) can relieve symptoms in patients with severe angina pectoris refractory to conventional medical or surgical therapy. This symptomatic improvement may result from decreased myocardial ischemia. To test this hypothesis, positron emission tomography (PET) and potassium-38 as a flow tracer were used in 8 patients for the quantitative evaluation of regional myocardial perfusion at rest and after exercise, before and during SCS. Potassium uptake was evaluated as myocardial clearance (flow times net extraction) in ml/min/100 g. Tomographic segments were categorized as nonaffected and affected on the basis of the absence or presence of arterial stenosis on coronary angiography and on the basis of thallium scintigraphic data. In nonaffected segments, before SCS, regional myocardial clearance significantly increased from rest (28 ± 4) to exercise (47 ± 13 clearance units; p <0.004). A similar increase occurred after SCS. In affected segments, before SCS, regional myocardial clearance barely increased (p = 0.065) from rest (26 ± 6) to exercise (33 ≤ 12). In comparison, after SCS, the resting regional myocardial clearance was slightly elevated (29 ± 8) reflecting an increased double product, but did not increase (p = 0.192) with exercise (34 ± 12). However, the magnitude and duration of ST-segment depression decreased during treatment with SCS. Anginal pain occurred in all patients during control exercise, but was attenuated in all but one with SCS. These results indicate that SCS improves exercise-induced angina and electrocardiographic signs of ischemia but this influence does not appear to be mediated by changes in regional myocardial perfusion.

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Spinal cord stimulation (SCS) has been used for the relief of neuralgic pain since its introduction in clinical practice by Shealy et al.[1] The mechanism explaining how SCS interferes with nociceptive nervous impulse propagation is still in debate, but might relate to the gate theory as proposed by Melzack and Wall.[2,3] This treatment appears effective in patients with peripheral vascular disease, in whom improvement in walking perimeter and in microvascular perfusion has been demonstrated.[4–6] SCS has also been used successfully to relieve symptoms of pain in patients with severe angina pectoris.[7] Mannheimer et al[7] and Sanderson[8] suggested that the antianginal effect of SCS in patients with coronary artery disease might be secondary to an anti-ischemic effect, and gave consideration to the possibility that this effect was related to changes in myocardial blood flow. Thus, the aim of the present study was to confirm the antianginal and anti-ischemic effect of SCS and to assess, using positron emission tomography (PET), whether these changes are mediated by an improved regional myocardial perfusion during exercise-induced angina pectoris.

Patients: Eight patients aged 53 to 71 years (mean 64) were selected for the study from a single institution, the Multidisciplinary Pain Center, Medical Department, Östra Hospital, Gothenburg. The epidural spinal stimulation electrodes were implanted in Gothenburg by the same surgeon as described earlier.[7] All patients had severe angina pectoris (Canadian Heart Association class III or IV) related to multivessel disease in 7 of 8 patients, and had been considered for surgery: 5 patients had previously undergone operation, 2 patients had refused surgery and the remaining patient was not considered suitable for surgery because of distal disease. Six patients had previous myocardial infarction. One, 2- and 3-vessel disease was present in 1, 3 and 4 patients, respectively. Left ventricular function was severely impaired in 2 patients. On thallium scintigraphic examinations ischemia involving the anterior or lateral wall, or both, of the myocardium was noted in all patients. Antianginal drugs except short-acting nitrates were discontinued 24 hours before the study in 6 of 8 patients. Stimulation of the spinal cord was applied for at least 2 months before the investigation, but SCS therapy was interrupted 48 hours before the investigation. The present study was approved by the ethical committees of both institutions. Patients were informed of the aims and procedures of the study and gave their consent.

METHODS

Experimental protocol: Unipolar stimulation was applied at the dorsal column at the T1–T2 level to achieve tolerable paresthesia covering the area of anginal pain cutaneous projection. Pulse width was 210 to 450 μs, frequency was 33 to 130 pps, amplitude range was 3.5 to 8.25 V.

PET was performed using a single-slice machine (ECAT II, Ortec, Oak Ridge, Tennessee). Potassium-38 was first injected at rest to define myocardial perfusion at baseline. After decay, a first bicycle exercise test was performed, starting at 50 W and increasing by 10 W/min, with the patient in the supine position on the bed of the tomographic camera. A second dose of potassium-38 was injected 1 minute before the end of exercise and imaging was begun 1 minute thereafter. A recovery scan was recorded 40 to 60 minutes after the end of exercise in 5 patients to document return to baseline conditions.

In the second part of the study, the epidural stimulation was switched on for 20 minutes followed by the injection of potassium-38 and recording of a new resting scan. Stimulation was continued and 30 minutes later a second supine exercise test was performed up to the same work load as during the first exercise test. Again, the tracer was injected 1 minute before the end of exercise and the last tomographic scans obtained. Overall, the procedure lasted 4 to 5 hours per patient.

Exercise and electrocardiographic data analysis: Arterial blood pressure (measured invasively) and the electrocardiogram (lead V_5) were monitored throughout the study. ST-segment alteration was considered abnormal if horizontal or downsloping depression (at least 1 mm) was observed. The following parameters measured with and without SCS were compared: exercise tolerance — duration of exercise, time of onset and duration of ST-depression, time of onset of angina pectoris; hemodynamic data — heart rate, systolic, diastolic and mean arterial pressure, product of heart rate and mean arterial pressure. These parameters were evaluated at rest (supine position), before exercise (supine position but with elevation of the legs), at the onset of ST-segment depression, at the onset of angina, at ST recovery, at angina recovery, at peak exercise and at comparable total work.

Tomographic data: Regional myocardial clearance of potassium-38 was calculated according to the following equation:

$$F \times E = \frac{CT(t) \times 100}{\int_0^t Ca(t)dt}$$

where F = flow, E = net extraction from time of injection to end of scan, CT(t) = myocardial tissue activity concentration, and Ca(t) = arterial blood activity concentration. PET with potassium-38 evaluates the product of flow times extraction (expressed in ml of blood/min/100 g of tissue) corresponding to the net clearance of potassium-38 from the blood to the myocardium. It is equal to the ratio of myocardial tissue activity [CT(t)] during the time interval of data collection to the integral of arterial blood activity [Ca(t)] assessed from the time of injection to the end of the scan, by continuous arterial withdrawal at a constant sampling rate. Calculation of the net myocardial clearance rate for potassium takes into account the fact that the single-pass extraction of potassium is incomplete and that the myocardial fixation of the tracer is not irreversible but that some secondary leakage of activity occurs.

Segmental analysis of the distribution of potassium-38 net clearance was performed using circumferential profile analysis. Nonaffected and affected segments were distinguished on the basis of coronary artery angiographic data and thallium-201 scintigraphy. Values for each segment were calculated as the mean of the circumferential profile analysis in 5 consecutive points in regions representative of each segment.

It is recognized that calculated values systematically underestimate regional myocardial clearance values as a result of partial volume effect.[9] However, no attempt was made to introduce a correction because it is impossible to measure myocardial wall dimensions in all directions and because quantification is also dependent on the homogeneity of the tracer uptake in the plane under study and in the contiguous planes.

As the object of this study was primarily to analyze changes in regional myocardial clearance from rest to exercise and from control to treatment, we believed that comparable relative measurements of regional myocardial clearance were adequate because they were reproducible and have been shown to follow directional changes of regional myocardial blood flow.[10]

Statistical analysis: Numerical results are presented as mean ± standard deviation. The differences between the values obtained before and after SCS were generally evaluated using paired *t* tests. For the analysis of differences related to angina, a Wilcoxon paired rank test was used because, in half of the population, angina disappeared completely in the SCS conditions. Differences were considered significant if the p value was <0.05 (using 2-sided tests).

RESULTS

Exercise tolerance: As determined by the experimental protocol, the work load achieved at the end of exercise was similar before and during SCS (84 ± 18 vs 86 ± 17 W). The exercise duration lasted roughly 7 minutes, in both conditions (425 ± 90 vs 440 ± 85 seconds). Angina occurred in all patients during control exercise with a latency of 215 ± 85 seconds. During exercise with SCS, symptoms of angina were attenuated in all patients but 1: The time to angina increased in 3 patients, no angina at all occurred in 4 subjects and the time to angina was slightly shorter with SCS in 1.

Clinical and electrocardiographic signs of ischemia: In control exercise, ST-segment depression was observed in 7 of 8 patients after a delay of 160 ± 128 seconds. ST-segment depression occurred in the same patients during exercise with SCS but, as a mean, with longer latency (244 ± 116 seconds; $p = 0.052$). The time of onset of ischemia increased in 5 patients and did not change in 2. The magnitude and duration of ST-

TABLE I Product of Heart Rate by Mean Arterial Pressure (beats/min × mm Hg)

Patient	Rest		Exercise		ST Depression	
	Before SCS	During SCS	Before SCS	During SCS	Before SCS	During SCS
1	5,800	8,540	20,001	21,780	13,883	18,954
2	6,693	7,104	12,017	16,244	12,467	13,108
3	7,104	7,929	15,180	14,605	14,145	14,547
4	11,037	12,508	25,407	25,200	*	*
5	6,613	9,368	14,472	17,355	14,472	17,355
6	7,597	7,440	11,484	12,818	*	*
7	8,107	9,936	15,958	16,811	†	†
8	10,920	11,689	17,941	16,872	14,620	16,427

*No recording of arterial blood pressure.
†No ST-segment depression.
SCS = spinal cord stimulation.

TABLE II Regional Net Clearance of Potassium-38 (ml/min/100 g)

Pt.	NA Segments Rest	Exercise	Recovery	Pt.	A Segments Rest	Exercise	Recovery
Before Spinal Cord Stimulation							
1	28	56		1	30	43	
2	33	51		2	33	36	
3	34	71		3	34	54	
4				4	28	23	27
5	25	38	26	5	25	33	28
6	29	32	30	6	21	19	22
7	25	39	26	7	20	22	18
8	25	44	26	8	20	35	20
During Spinal Cord Stimulation							
1	42	65		1	36	46	
2	40	49		2	38	41	
3	34	63		3	34	47	
4				4	30	16	
5	36	48		5	35	44	
6	30	35		6	21	20	
7	25	36		7	22	25	
8	24	45		8	19	34	

A = affected; NA = not affected.

segment depression at maximal comparable work load decreased during treatment with SCS (−2.0 ± 0.4 vs −1.4 ± 0.3 mm [$p < 0.025$], and 15.0 ± 4.1 vs 9.2 ± 5.0 minutes [$p < 0.05$], respectively).

Hemodynamic parameters during control and treatment with spinal cord stimulation (Table I): At rest, at the time of the PET measurement, heart rate and heart rate–blood pressure product were higher during SCS ($p < 0.05$). However, immediately before exercise, in the supine position with legs up, hemodynamic parameters were similar in control and SCS conditions. At maximal comparable work load, heart rate–blood pressure product was higher during SCS, although not significantly (16,078 ± 2,302 vs 13,917 ± 860; $p = 0.064$). At the time of onset of ST-segment depression, again heart rate–blood pressure product was higher during SCS although not significantly ($p = 0.113$).

Regional myocardial net clearance of potassium-38 during control and treatment with spinal cord stimulation (Table II): At rest, regional myocardial net clearance of potassium-38 increased insignificantly during SCS both in nonaffected and in affected segments ($p = 0.094$ and 0.058, respectively). During exercise, no significant difference ($p = 0.582$) was recorded between control and SCS in the affected ($p = 0.654$) or nonaffected ($p = 0.582$) segments. For instance, in a study performed in a patient with severe proximal stenosis of the left anterior descending artery and occlusion of the right coronary artery, the distribution of potassium-38 is similarly altered at rest, in the anterior wall and at a lesser degree in the septum, during both control and SCS (Figure 1). At exercise, the net potassium-38 clearance decreases in the anterior wall in both conditions, contrasting with the increased tracer clearance in

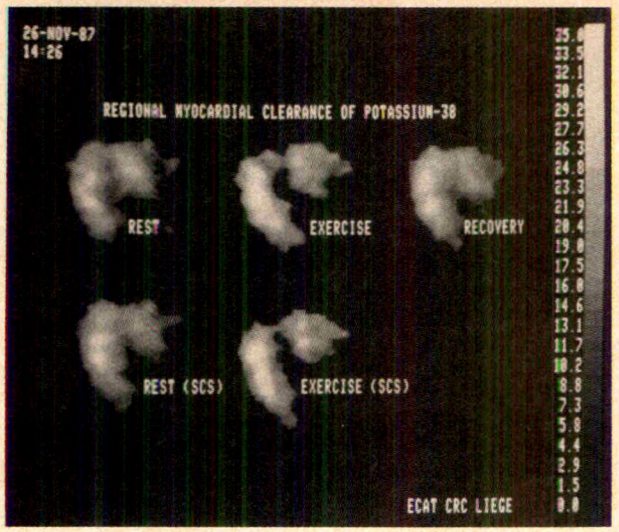


FIGURE 1. Tomograms recorded before and during spinal cord stimulation (SCS) in a patient with severe 2-vessel disease. The anterior wall and the septum are the most affected regions of the left ventricle. The distribution of potassium-38 is similar before and during SCS.

the nonaffected lateral wall. The scan recorded 40 minutes after the first exercise test shows that the distribution of potassium-38 has recovered back to the control values, before the application of SCS.

Figure 2 represents the values of potassium net clearance obtained in control, in 5 regions of interest (posterolateral, anterolateral, anterior, anteroseptal and posteroseptal). From rest to exercise, the net clearance of potassium-38 increases in the nonaffected lateral segments and decreases in the affected segments. At recovery, the clearances of the cation were similar to the values observed at rest. Figure 3 shows the results obtained with the neurostimulator switched on. The diminution of potassium-38 clearance appears slightly more pronounced in the anterior wall and the anteroseptal region supplied by the left anterior descending artery, while in the posterolateral and anterolateral segments, the net clearance increases as in the control situation.

Figures 4 and 5 illustrate individual segmental clearance variations in the affected segments before and during stress. Before stimulation, clearance increased in 13 segments and decreased in 9. During SCS, clearance increased in 14 segments, decreased in 7 and remained

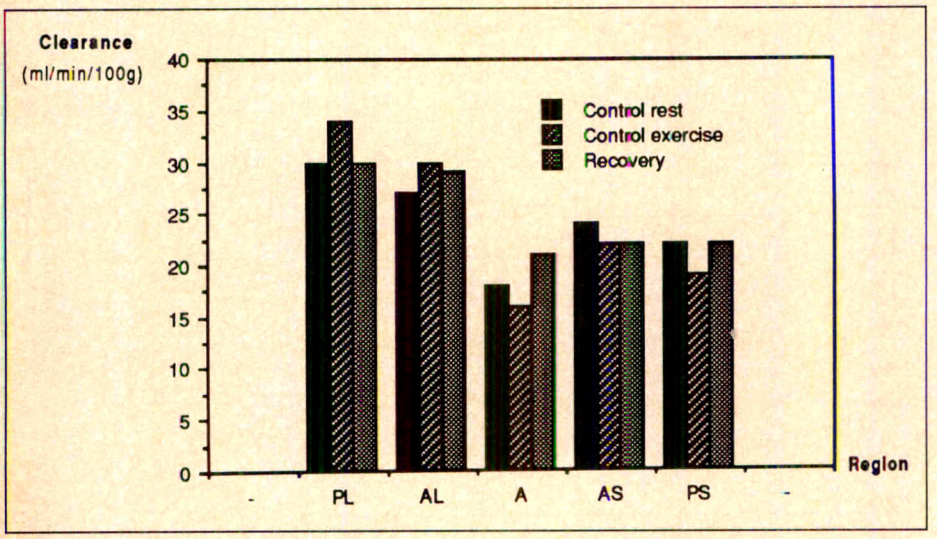


FIGURE 2. Clearance of potassium-38 in control conditions calculated in 5 regions of interest in 1 patient (see Figure 1). Clearance increased from rest to exercise in lateral segments and decreased in anterior wall and septum. During recovery, clearance is similar to rest. A = anterior; AL = anterolateral; AS = anteroseptal; PL = posterolateral; PS = posteroseptal.

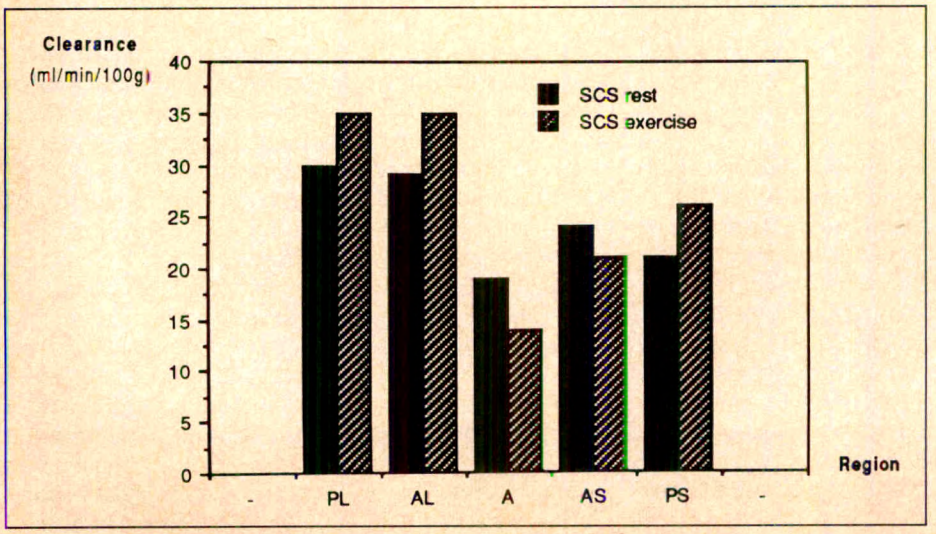


FIGURE 3. Clearance of potassium-38 during spinal cord stimulation (SCS) calculated in the same patient. The decrease of clearance appears slightly more pronounced in the anterior wall than in control. Other abbreviations as in Figure 2.

constant in 1. These data therefore do not suggest that SCS results in changes in regional myocardial perfusion during exercise.

DISCUSSION

Earlier studies with transcutaneous electrical nerve stimulation and SCS have demonstrated increased work capacity, reduced frequency of anginal attacks, reduced consumption of short-acting nitrates together with decreased evidence for myocardial ischemia (decreased ST-segment depression on serial bicycle exercise tests).[7,8,11–13]

Hemodynamic studies of the effect of transcutaneous electrical nerve stimulation and SCS have shown increased tolerance to atrial pacing-induced angina and improved myocardial lactate metabolism at comparable heart rate, because lactate production during control changed to lactate extraction during treatment.[12–14] However, at maximal pacing rates during stimulation, lactate production was again observed and all patients experienced pain at that time. This indicates that myocardial ischemia is not concealed when present. Stimulation does not seem to deprive the patient of a warning signal.

These observations of transcutaneous electrical nerve stimulation and SCS efficacy on symptomatic and objective evidence of myocardial ischemia were confirmed in this study. Indeed, in control conditions, we observed a low tolerance to supine bicycle exercise confirming disease severity: Angina occurred in all patients at a low work load, and electrocardiographic signs of ischemia were present. SCS in these patients resulted in beneficial effects manifest as decreased or abolished anginal pain, decrease in pain duration and decreased magnitude and duration of ST-segment depression.

Patients with chronic conditions, in whom optimal medical therapy had failed to relieve angina, had been successfully managed by SCS for ≥2 months before the PET investigation. To study patients in "basal conditions," SCS was discontinued for 2 days before. The

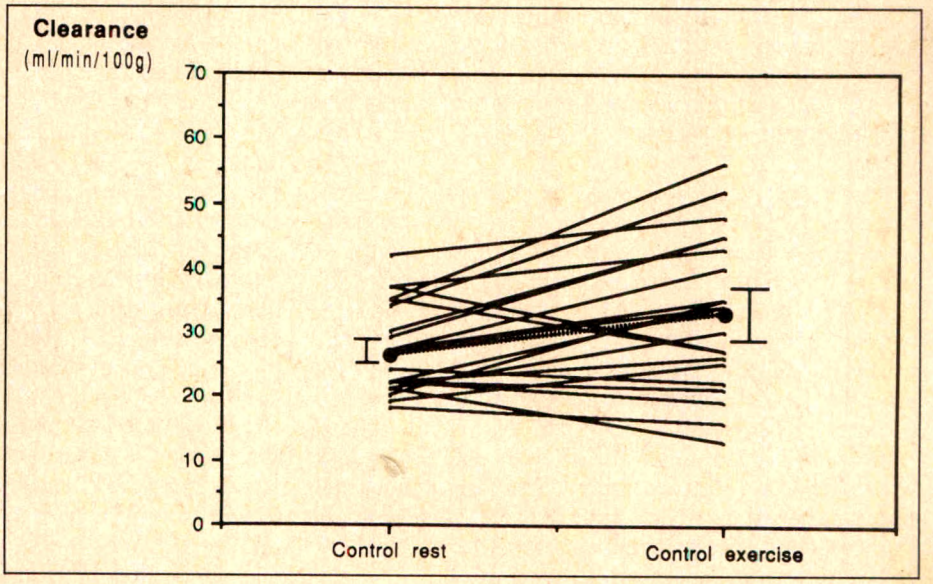


FIGURE 4. Segmental distribution of potassium-38 in affected segments (control conditions). From rest to exercise, the clearance of potassium-38 increases in 13 segments and decreases in 9 other segments. Mean values are represented by *closed circles;* standard errors of the mean are also shown.

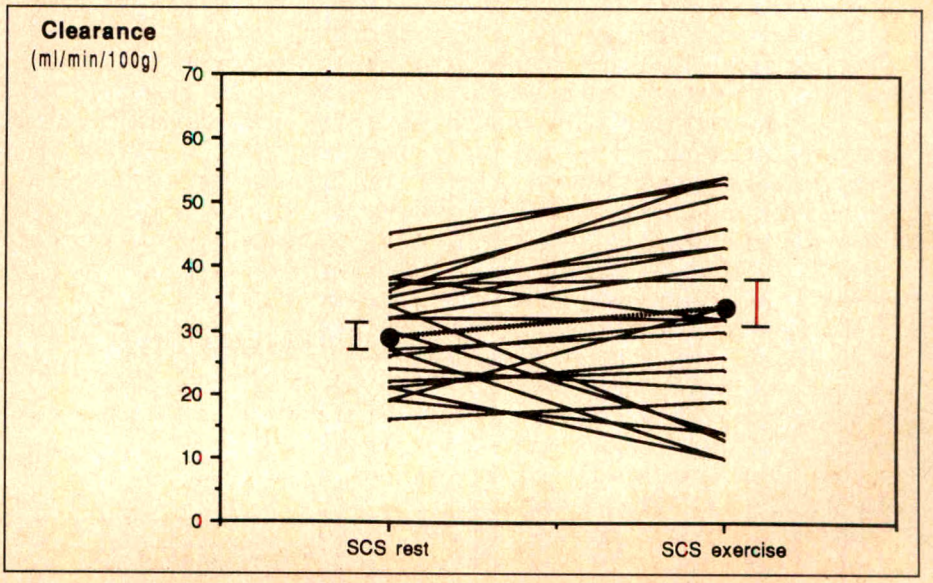


FIGURE 5. Segmental distribution of potassium-38 in affected segments (during spinal cord stimulation [SCS]). From rest to exercise, the clearance of potassium-38 increases in 14 segments, is diminished in 7 and remains constant in 1. As a whole, segmental variations of clearance are similar to those observed in Figure 4. Mean values are represented by *closed circles;* standard errors of the mean are also shown.

sequence of testing, rest/stress control, rest/stress with stimulation could not be altered because we do not know the duration of the therapeutic effects after interruption of SCS. Furthermore, it is impossible both for the patient or investigator to be unaware of the presence of stimulation since stimulation produces paresthesia and interferes with the electrocardiogram. To document return to baseline after the first exercise test, we performed a "recovery" scan 40 to 60 minutes after the first exercise in the last 5 patients. In all cases, such recovery was confirmed.

The mechanism for symptomatic improvement and potential anti-ischemic effect of SCS is not known, but could theoretically result from increased coronary blood flow, decreased myocardial oxygen demand or a direct pain-inhibiting effect, or all 3 of these.

The present study was set up to evaluate the effects of SCS on regional myocardial blood flow but failed to show any significant changes during exercise. It is therefore important to analyze the design and methods used to evaluate its significance. Patients selected had disease and ischemia located in the left anterior descending or left circumflex territory as documented by coronary angiography and previous thallium imaging for optimal visualization of the abnormalities in the tranverse planes available with a single-slice PET machine.

We chose potassium-38 as the perfusion tracer because its 7.7-minute half-life permitted the acquisition of 2 to 3 slices per injection as well as to repeat studies within 30 minutes. It gives excellent images of the myocardium without lung uptake in smokers, as is the case with ammonia, and can be produced at regular intervals to accommodate a complex protocol. Potassium-38 does not measure flow but flow times extraction or regional myocardial clearance, a parameter directionally related to flow. Underestimation of flow with this technique is unavoidable and results mainly from changes in extraction values and partial volume effect, and potentially (although less likely in patients with reversible ischemia) from secondary potassium leakage.[15-17]

We therefore believe that regional myocardial clearance measurements, as performed, accurately reflect directional changes in regional myocardial perfusion and adequately correlate to it in the low to normal flow range. Such measurements can document exercise-induced perfusion abnormalities as well as spontaneous or therapeutic improvement. Therefore although small localized changes might not be appreciated, clinically significant changes are unlikely to be missed.

Results of this study demonstrated lack of improvement during SCS, compared with the control exercise situation. However, changes were observed at rest, and their significance is not entirely clear because they were accompanied by an increase in heart rate. These hemodynamic changes, only present during supine rest and not confirmed just before bicycling, might have resulted from the fatigue and discomfort of the long protocol rather than from the stimulation itself.

Because SCS does not appear to improve regional myocardial blood flow during exercise, what of the alternative potential mechanisms? Decreased oxygen consumption does not seem to result from systemic hemodynamic changes because the heart rate–blood pressure product was not modified by SCS. However, regional cardiac hemodynamic changes could be involved. Indeed, we did not measure the ventricular volumes, but a decrease in left ventricular volume could diminish wall stress in the absence of changes in heart rate–blood pressure product. One may also speculate that local changes could decrease myocardial contractility and thereby oxygen demand, and postpone the occurrence of myocardial ischemia and the increase in oxygen demand secondary to ventricular dysfunction.

The presence of opiate receptors as well as of short opioid peptides like enkephalin and dynorphin has been demonstrated in the myocardium in several animal studies.[18-19] Enkephalin-related peptides are found and stored in the sympathetic nerve-endings in the myocardium. They are released during stress and are supposed to have an inhibitory effect on sympathetic nerve terminals in the heart.[20] In 1 investigation presented by Mannheimer et al.[21] in abstract form (1991), it was shown that the human myocardium has the ability to release β-endorphin, enkephalins and dynorphin. There was also an increased myocardial release of enkephalin and β-endorphin in all 5 patients studied. Animal studies have shown that enkephalins exert a local inhibitory effect on the sympathetic activity in the myocardium and by this mechanism decrease myocardial oxygen demand.

In 1 study, Kröger et al[22] demonstrated that acute somatic pain induced ischemic myocardial dysfunction distal to a severe coronary stenosis by a local activation of cardiac sympathetic nerves. The analgesic agent fentanyl not only prevented the pain manifestation, but also the poststenotic myocardial ischemia. Furthermore, Blomberg et al[23] demonstrated that in addition to its antianginal effect, cardiac sympathetic blockade with regional thoracic epidural anesthesia in humans seemed to have a favorable effect on myocardial ischemia and may also offer a protection against ischemia-induced ventricular arrhythmias.

Finally, the possibility of a placebo effect must be considered because neither the patient nor the physician can be unaware of the effects of stimulation and because surgical procedures are especially likely to produce such an effect.[24] However, the fact that there were objective signs of reduced ischemia makes it reasonable to assume that physiological mechanisms other than placebo effects are of importance.

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Usefulness of Single-Photon Emission Computed Tomography of Thallium-201 Uptake After Dipyridamole Infusion for Detection of Coronary Artery Disease

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The diagnostic performance of single-photon emission computed tomography (SPECT) and planar imaging of thallium-201 uptake for the detection of coronary artery disease (CAD) was compared in 79 patients who underwent both dipyridamole thallium-201 scintigraphy and coronary angiography. Clinical subgroups were assigned by severity of CAD, presence of a prior myocardial infarction and the number of narrowed coronary arteries. The overall detection of CAD was 89% for SPECT and 67% for planar ($p < 0.001$). For the anterior vascular territory, sensitivities for SPECT and planar imaging were 69 and 44% ($p < 0.01$), respectively; for the posterior vascular territory, sensitivities were 80 and 54% ($p < 0.01$). Receiver-operating characteristic analysis, using a 5-point evaluation scale, was performed for the anterior and posterior vascular territories. Receiver-operating characteristic curves generated for SPECT and planar studies demonstrated improved diagnostic performance by SPECT in the anterior vascular territory, but showed similar performance in the posterior territory because of lower SPECT specificity despite higher sensitivity at clinically relevant decision thresholds. In each clinical subgroup of patients, the detection of CAD by SPECT was significantly superior to that by planar imaging, regardless of the severity of stenosis or the number of significantly narrowed coronary arteries, or whether a myocardial infarction was present. Thus, SPECT thallium-201 scintigraphy is an important and necessary clinical tool for detecting CAD after dipyridamole infusion.

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Exercise stress testing has been used to provoke ischemia in patients with suspected or known coronary artery disease (CAD)[1] and to stratify risk of cardiac events in patients with known CAD before surgery.[2] The addition of thallium-201 scintigraphy to assess differences in myocardial perfusion has increased sensitivity, specificity and diagnostic accuracy of the exercise stress test.[3] However, the sensitivity of thallium exercise stress testing is dependent on the level of exercise achieved.[4] For patients with CAD who are unable to exercise[5] adequately to an ischemic end point, intravenous dipyridamole, a potent vasodilator, has been used in conjunction with thallium-201 in these patients as an alternative to exercise stress testing,[6–11] with sensitivities and specificities similar to conventional exercise stress testing for detection of CAD.[8,12,13]

Single-photon emission computed tomography (SPECT) of thallium-201 uptake after rest[14] and exercise[15,16] improves sensitivity and specificity for the detection of CAD compared with planar imaging.[15] The use of SPECT after dipyridamole has not been rigorously compared with planar imaging for the detection of CAD; therefore, we compare the diagnostic performance of SPECT and planar thallium-201 imaging for the overall detection of CAD in the individual vascular territories. Patients who had undergone both dipyridamole thallium scintigraphy and cardiac catheterization were evaluated with respect to severity of vessel stenosis, extent of coronary artery involvement, and the presence or absence of a myocardial infarction.

METHODS

Patient selection: Seventy-nine patients with known or suspected CAD underwent dipyridamole thallium-201 scintigraphy within a mean of 14 days of cardiac catheterization from the period of September 1985 through May 1988.* Patients with unstable angina or severe bronchospastic disease receiving aminophylline preparations were excluded from dipyridamole thallium-201 testing. The decision for cardiac catheterization was made by the patient's attending physician for clinical indications. Patients were excluded from this analysis if myocardial infarction, coronary revascularization, or if clinical deterioration had occurred between the time of dipyridamole thallium-201 testing and cardiac catheterization.

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Dipyridamole infusion protocol: All patients gave informed consent. With the patient supine, an intravenous catheter was inserted into an arm vein. Electrocardiographic leads were placed in standard exercise locations. Baseline heart rate, blood pressure and 12-lead electrocardiograms were recorded and repeated at 1-minute intervals during and for 6 to 10 minutes after infusion. Dipyridamole, 0.56 mg/kg, was infused over 4 minutes through a Harvard infusion pump under the supervision of a cardiologist. Aminophylline was immediately available for intravenous administration in the event of chest pain or other symptoms.

Thallium-201 scintigraphy protocol: Three mCi (111 MBq) of thallium-201 were administered 4 minutes after the completion of dipyridamole infusion. Planar image acquisition began 3 to 10 minutes after thallium-201 administration in the anterior, 35° left anterior oblique and 70° left anterior oblique projections. Planar thallium-201 imaging was performed using a gamma camera equipped with a low-energy, all-purpose parallel hole collimator. Each image was acquired for 5 minutes and consisted of approximately 750,000 counts. Following planar imaging, SPECT acquisition was performed over a 180° arc from the right anterior oblique to the left posterior oblique projection using a noncircular orbit with 64 angular samples obtained at 20 seconds per projection. Images were reconstructed using a filtered back-projection algorithm. Tomographic data were presented in horizontal long-axis, vertical long-axis and short-axis slices. The images were recorded on 8 × 10 inch x-ray film. Redistribution images were acquired 3 hours later using the same protocol.

Thallium-201 image assessment: Immediate and delayed thallium-201 planar images were interpreted by experienced observers unaware of patient identity, and clinical and angiographic findings. Paired SPECT images were assessed in the same manner at a different reading session. Differences were resolved by consensus. The severity of disease was assessed using a 5 point scale: (1) definitely normal, (2) probably normal, (3) equivocal, (4) probably abnormal, and (5) definitely abnormal. An abnormal study was defined as either 4 or 5 ("strict" criteria) or with the addition of equivocal scans 3, 4 or 5 ("liberal criteria"). For the purpose of scintigraphic analysis (Figure 1), vascular territories were divided into the anterior circulation, the myocardium supplied by the left anterior descending artery, and the posterior circulation supplied by the right and left circumflex coronary arteries.

Coronary angiography: Cardiac catheterization was performed after an overnight fast using either standard Judkins or Sones technique. Coronary angiography was obtained in multiple orthogonal projections and single or biplane left ventriculograms were performed.

Assessment of cineangiograms: Cineangiograms were evaluated by an experienced angiographer unaware of both clinical and scintigraphic data. Vessel diameter stenosis was estimated visually using a 5 point scale: (0) normal, (1) 0 to 49% stenosis, (2) 50 to 69% stenosis, (3) 70 to 99% stenosis, and (4) 100% artery occlusion. The severity of wall motion abnormalities was assessed using a 4 point scale: (1) normal, (2) hypokinetic, (3) akinetic, and (4) dyskinetic. CAD was defined as a stenosis of ≥70% lumen diameter narrowing or a wall motion abnormality and a history of a myocardial infarction. Mild stenosis was defined as a vessel narrowing of 50 to 69%. Extent of CAD was defined as the number of vessels with stenosis of ≥70%. Myocardial infarction was defined by clinical history or electrocardiographic evidence of a myocardial infarction.

Statistics: Categorical data comparisons of sensitivities were made by chi-square analysis. Specificity could not be assessed for overall detection of CAD because of the high prevalence of CAD in our study population. Specificity could be determined for individual vascular territories. Receiver-operating characteristic curves were generated using the CORROC program of Metz.[17] Statistical differences between receiver-operating characteristic curves employed the area test.[17] Differences were considered significant at $p < 0.05$.

RESULTS

Patient characteristics: The 79 patients in the study had a mean age of 60 ± 11.1 years (range 33 to 83) and 73% were men. There was evidence of CAD in 96% of the patients: 70% (55) had a prior myocardial infarct and 75% had at least 1 artery with a lumen diameter narrowing of ≥70%. The distribution of CAD in the individual vascular territories was nearly identical for men and women. There were 18 patients who had either noncritical coronary disease or a patent vessel but had a wall motion abnormality and a history of myocardial infarction. Of these, 4 had 50 to 69% stenosis in at least 1 vessel and the remainder had <49% stenosis. The incidence of ischemic electrocardiographic changes, symptoms and use of aminophylline was similar to that previously published.[6–13]

Scintigraphic results: overall disease detection and individual vascular territories: Using strict criteria, an abnormal scintigraphic study was defined as definitely

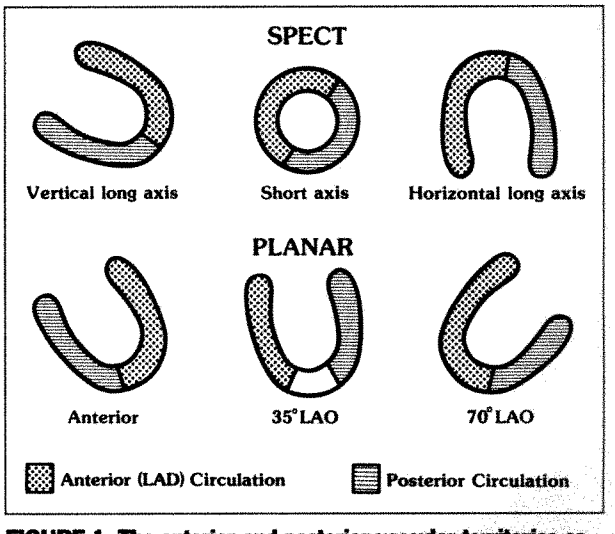


FIGURE 1. The anterior and posterior vascular territories assigned for thallium-201 single-photon emission computed tomography (SPECT) and planar scintigraphy evaluation after dipyridamole infusion. The unassigned vascular territory in the 35° left anterior oblique (LAO) projection is an area with variable blood supply. LAD = left anterior descending artery.

TABLE I Overall Disease Detection

Vascular Territory	Strict Criteria (4, 5) Planar #/Total (%)	Strict Criteria (4, 5) SPECT #/Total (%)	Liberal Criteria (3, 4, 5) Planar #/Total (%)	Liberal Criteria (3, 4, 5) SPECT #/Total (%)
A. Detection of Coronary Artery Disease: Sensitivity				
Overall	51/76 (67)	68/76 (89)‡	68/76 (89)	74/76 (97)*
Anterior	23/52 (44)	36/52 (69)†	38/52 (73)	45/52 (85)†
Posterior	32/59 (54)	47/59 (80)†	48/59 (81)	51/59 (85)
B. Exclusion of Coronary Artery Disease: Specificity				
Anterior (n = 27)	26/27 (96)	27/27 (100)	17/27 (63)§	22/27 (81)
Posterior (n = 20)	19/20 (95)‖	14/20 (70)	12/20 (60)‖	8/20 (40)

SPECT versus planar: *p <0.05; †p <0.01; ‡p <0.001.
Strict versus liberal criteria for assessment: §p <0.01; ‖p <0.05.
SPECT = single-photon emission computed tomography.

("5") or probably ("4") abnormal (Table IA). The overall detection of CAD by SPECT was 89% compared with 67% by planar scans (p <0.01). When the detection of CAD was evaluated for the individual vascular territories, the detection of disease in the anterior vascular territory (left anterior descending artery) by SPECT was 69% compared with 44% by planar scans (p <0.01). It was thought to be a useful clinical designation to assess the right coronary and left circumflex arteries as a combined posterior vascular territory since the patients studied had both right and left dominant coronary artery circulations. In the posterior circulation, SPECT had a sensitivity of 80% compared with 54% by planar studies (p <0.01).

When the comparison was performed with more liberal ("3–5") criteria, planar scanning in the anterior vascular territories had a sensitivity of 73% for detection of a defect compared with 86% with SPECT (p <0.01). In the posterior vascular territory, when the liberal criteria were used, planar and SPECT had similar sensitivities of 81 and 87%, respectively. Therefore, when planar scans were read incorporating "equivocal" studies as abnormal or positive, the sensitivity for detection of CAD approached that of SPECT at a strict decision threshold.

Table IB demonstrates specificity in the individual vascular territories. Specificity improved when strict criteria were used. This improvement was significant for planar scans. Specificity for SPECT was high and there was no statistical difference using either strict or liberal criteria. Overall specificity for SPECT decreased in the posterior vascular territory.

Receiver-operating characteristic analysis: Diagnostic accuracy for detection of disease in the anterior and posterior vascular territories was evaluated by generating receiver-operating characteristic curves. Each operating point represents the sensitivity/specificity pair generated at a particular decision threshold. For anterior circulation, SPECT demonstrated improved diagnostic performance at multiple decision thresholds compared with planar scintigraphy (Figure 2A). Figure 2B displays the SPECT and planar receiver operating characteristic curves for the posterior circulation. At most decision thresholds for the posterior circulation, SPECT

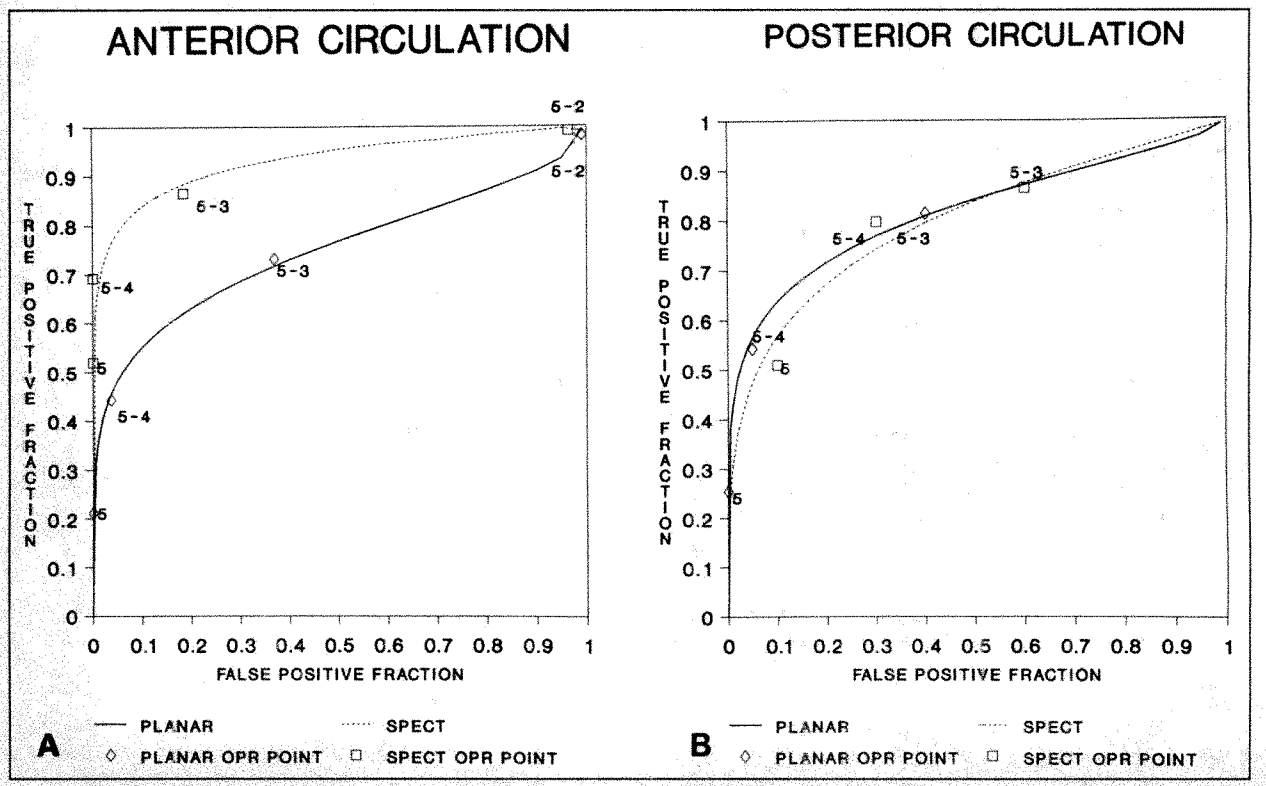


FIGURE 2. ***A*, receiver-operating characteristic curve for diagnosis of coronary artery disease in the anterior vascular territory. *B*, receiver-operating characteristic curve for diagnosis of coronary artery disease in the posterior territory. OPR = operating; SPECT = single-photon emission computed tomography.**

achieved higher sensitivity but lower specificity than planar imaging. The nearly superimposable receiver-operating characteristic curves demonstrate similar diagnostic performance. This pattern is similar to that previously described with exercise thallium tomography.[15] Receiver-operating characteristic analysis could not be performed for the overall detection of CAD because of the small number of patients without CAD in the study cohort. For this reason, receiver-operating characteristic curves could also not be generated for the subset analyses of the nature and extent of CAD as well as the presence of prior myocardial infarction.

Presence of prior myocardial infarction: The detection of CAD defined as a stenosis of ≥70% in the presence or absence of a prior myocardial infarction is depicted in Table IIA. A history of a prior myocardial infarction was present in 55 patients (70%). SPECT had significantly improved sensitivity in the presence of a myocardial infarct compared with planar scintigraphy: 93 vs 75% ($p < 0.01$). Even in the absence of a prior myocardial infarction, SPECT had an improved sensitivity for detection of disease of 81% compared with 50% for planar imaging ($p < 0.05$).

Severity of coronary artery stenosis: Angiographically critical disease defined as ≥70% luminal narrowing of at least 1 artery was found in 59 patients (75%). In these patients, SPECT had significantly improved disease detection 90% compared with 69% for planar imaging ($p \leq 0.01$). As CAD is a diffuse process, there may be clinically significant disease of ≤50 to 69% stenosis, which may not be considered angiographically critical. Coronary artery narrowing of lesser degrees was found in only 12 patients (15%), in whom detection of disease was 83% for SPECT and 58% for planar imaging. This difference did not achieve statistical significance because of the small sample group size (Table IIB).

Extent of coronary artery disease: The overall detection of CAD in patients with single or multivessel involvement (stenosis ≥70%) is summarized in Table IIC. In the 33 patients with stenosis in only 1 coronary artery, CAD was detected with 88% sensitivity by SPECT compared with 58% by planar imaging ($p < 0.01$). In the 43 patients with significant luminal stenoses in >1 coronary artery, SPECT had improved sensitivity of 91% compared with planar sensitivity of 74% ($p < 0.05$).

TABLE II Detection of Coronary Artery Disease: Disease Severity (SPECT vs planar)

Disease Severity	SPECT #/Total (%)	Planar #/Total (%)
A. Myocardial infarction		
Absent	18/22 (82)*	11/22 (50)
Present	51/55 (93)†	41/55 (75)
B. Most severe vessel stenosis		
50–69% stenosis	10/12 (83)	7/12 (58)
≥ 70% stenosis	53/59 (90)†	41/59 (69)
C. Extent of coronary artery disease		
Single-vessel disease	29/33 (88)†	19/33 (58)
Multivessel disease	39/43 (91)*	32/43 (74)

*$p < 0.05$ SPECT vs planar.
†$p < 0.01$ SPECT vs planar.
SPECT = single-photon emission computed tomography.

DISCUSSION

The results of this study demonstrate improved sensitivity for detection of CAD by SPECT thallium-201 scintigraphy compared with planar imaging after dipyridamole infusion. This superiority extended to specific vascular beds at comparable decision thresholds; when subjected to receiver-operating characteristic analysis, the superiority of SPECT was only noted for the anterior vascular territory.

Previous studies: This study analyzes dipyridamole use with SPECT thallium-201, whereas previous studies have evaluated SPECT thallium-201 after exercise stress testing.[15] Dipyridamole has been used in conjunction with thallium-201 scintigraphy as an alternative to conventional exercise thallium stress testing.[2,6,8-11] There are many patients with suspected CAD who cannot adequately exercise because of vascular, orthopedic, neurologic or pulmonary limitations, and who can be evaluated for the presence of CAD by intravenous dipyridamole with thallium-201 scintigraphy. For myocardium perfused by a stenosed coronary artery, reduction in perfusion pressure may occur and blood flow either decreases or is unchanged compared with the increased flow in normally perfused myocardial regions due to dipyridamole vasodilatation. The overall detection rate of CAD by dipyridamole thallium scanning is comparable to that of exercise thallium imaging[9,12] ranging from 67[12] to 93%.[18] However, comparison of these studies are limited due to varying definitions of CAD with luminal stenoses of ≥50[12] to ≥70%.[8]

Planar versus SPECT thallium-201 scintigraphy: Planar dipyridamole thallium scintigraphy is subject to some of the same imaging limitations encountered with exercise thallium-201 studies. These include breast attenuation, which hinders visualization of defects in the upper septum and inferior walls and apical thinning in the scintigraphic image, which may be a normal variant. Although not immune to the effects of attenuation, SPECT reduces imaging problems due to these artifacts and the effect of overlapping myocardial structures. Previous studies have shown SPECT to be superior in detecting CAD compared with conventional planar thallium-201 after exercise.[15,16] Our data demonstrate similar improved diagnostic performance for SPECT after dipyridamole infusion. The first published report of tomographic imaging after dipyridamole infusion used a 7 pinhole collimator to detect coronary stenoses of ≥70% and reported comparable sensitivities for planar and tomographic imaging of 78 and 72%,[8] respectively. These forms of limited angle tomography are less widely available, and are subject to additional artifacts and are more difficult to perform than SPECT. In a more recent study, DePuey et al[19] performed SPECT using bulls-eye maps, which demonstrated a sensitivity of 89% for detection of ≥50% stenosis of any vessel, but comparison to planar imaging was not performed.

Receiver-operating characteristic curves: Receiver-operating characteristic curves were generated to define

diagnostic performance for SPECT and planar imaging in the anterior and posterior vascular territories. In this analysis, true-positive fraction represents sensitivity and is displayed on the Y-axis of the receiver-operating curve unit square. The false-positive fraction refers to 1−specificity and is displayed on the X-axis of the receiver-operating curve unit square. The ideal receiver-operating characteristic curve, which characterizes optimal diagnostic performance, is shifted upward into the left hand corner of the receiver-operating characteristic unit square. The SPECT receiver-operating characteristic curve for the anterior circulation (Figure 2A) demonstrates significantly improved diagnostic performance; planar imaging achieved the sensitivity of SPECT but at significantly lower specificity. The receiver-operating characteristic curves for posterior circulation (Figure 2B) demonstrate no difference between the diagnostic performance of SPECT and planar studies. Although SPECT demonstrates greater sensitivity at each decision threshold, this is achieved at a lower specificity, implying similar overall diagnostic performance. Therefore, liberal (5–3) diagnostic criteria should be avoided when assessing the posterior circulation because of the substantial loss in specificity similar to that reported for SPECT and planar imaging of thallium-201 uptake after exercise.[15]

Study limitations: Because of the high incidence of CAD in this patient population, overall specificity for the detection of significant CAD could not be accurately assessed. In the individual vascular territories, both sensitivity and specificity could be evaluated. The high incidence of CAD was a result of pretest screening by cardiologists and the fact that cardiac catheterization was performed at the discretion of the attending cardiologist. In this study, CAD was defined as ≥70% stenosis. In prior studies using these criteria, diagnostic accuracy of thallium-201 scintigraphy after dipyridamole had ranged from 59[8] to 81%,[11] with a slightly higher incidence of 91%[9] when CAD was defined ≥50% stenosis. The high incidence of patients who have had prior myocardial infarction contributed to the high incidence of CAD in this study. This reflects the clinical practice at our institution, that dipyridamole thallium testing is often used for postmyocardial infarction evaluation as previously reported by others.[20]

Data from animal studies suggest that redistribution cannot be as rapid after dipyridamole in areas subserved by a stenotic vessel.[18] Therefore, the slight delay in SPECT image acquisition, which always followed planar images, should not have altered our results.

Sensitivity for the detection of CAD in the individual vascular territories by thallium-201 scintigraphy was decreased[15,16,19,21] as confirmed by our data. Specifically, the vascular supply of the inferior and lateral walls derives from the right coronary or left circumflex arteries, either of which may be dominant. Because of the clinical impact of this anatomic variance on the results, we divided the myocardium into anterior and posterior vascular territories. There was only 1 patient with isolated left circumflex artery disease; therefore, in most patients with circumflex CAD there were also lesions in other arteries. With thallium-201 myocardial perfusion imaging, the most severe vessel lesion may obscure visualization of decreased perfusion in another vessel territory, since visual analysis consists of comparing the relative activity in various regions of the myocardium.

Specific problems in diagnosis of significant CAD in the right coronary artery have been addressed by others.[15,21] There may be normally decreased uptake in the inferobasal segment.[15] This has been attributed to greater attenuation, overlap of valvular structures and tomographic slices that may exclude myocardium in some sections.[15] The inferobasal wall may be supplied by a dominant right coronary artery or by a dominant left circumflex artery branch. Therefore, the inferobasal segment was designated as part of the posterior vascular territory.

Last, in this analysis, qualitative visual assessment was used. Most studies of thallium-201 scintigraphy after dipyridamole infusion have used qualitative analysis of images.[9,11–13] Other investigators using quantitative analysis have demonstrated improved sensitivity.[8,19,22] If quantitative methods had been used in this study, sensitivity may have been further increased.

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Efficacy of a Single Dose of Slow-Release Isosorbide Dinitrate in the Treatment of Silent or Painful Myocardial Ischemia in Stable Angina Pectoris

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A double-blind study was performed in 32 patients with stable angina pectoris to assess the effects of slow-release isosorbide dinitrate (ISDN) (a single dose of 120 mg/day) on the frequency and duration of painless and painful ischemic episodes, and on electrocardiographic changes and exercise tolerance. Forty-eight-hour electrocardiographic monitoring and treadmill exercise tests were performed before, and at 20 and 21 days of therapy. Holter monitoring showed a significant decrease in the frequency of painful and silent episodes ($p < 0.001$), and in the duration of painful (1,623 ± 664 seconds vs 323 ± 161 seconds; $p < 0.001$) and silent episodes (2,818 ± 1,496 seconds vs 223 ± 102 seconds; $p < 0.001$). The magnitude of painful and silent ST-segment depression was significantly reduced (2.7 ± 0.9 mm to 0.7 ± 0.7 mm and 2.0 ± 1.1 mm to 0.7 ± 0.5 mm, respectively; $p < 0.001$). Time of exercise testing to the onset of ST-segment depression (442 ± 137 seconds vs 858 ± 110 seconds; $p < 0.001$) or anginal pain was doubled (461 ± 128 seconds vs 830 ± 130 seconds; $p < 0.001$). The work load increased from 6 to 10 METs ($p < 0.001$). ISDN in a single dose of 120 mg/day is a valuable drug for stable angina pectoris, decreasing the frequency of silent and painful ischemic episodes and the magnitude of ST-segment depressions, and increasing exercise tolerance. It particularly shortened the duration of silent episodes. For patients' compliance, a once-daily dose of ISDN could be advantageous.

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Silent myocardial ischemia as a frequent and prognostically adverse event in ischemic heart disease has been well documented by various investigators. For its treatment they propose drugs that have proved efficacious in the classic forms of myocardial ischemia, namely nitroglycerin derivatives, calcium antagonists and β-adrenergic receptor blockers.[1–10] Silent myocardial ischemia has been found to occurs frequently in stable angina pectoris despite conventional antianginal drug therapy.[11]

Although various studies indicate that nitroglycerin derivatives are efficacious in the treatment of various angina syndromes, their role in the management of silent ischemia is not entirely defined.[1,2,12] The purpose of this study was to compare the incidence of silent and painful myocardial ischemia in patients with stable angina pectoris during 48-hour electrocardiographic monitoring and treadmill exercise testing before and after 120 mg of slow-release isosorbide dinitrate (ISDN) (Isoket, Schwarz Pharma, Monheim) or placebo given in a single dose (once daily).

METHODS

The study group consisted of 32 patients (26 men and 6 women, average age 51 years [range 39 to 62]) including 25 with a previous myocardial infarction experienced ≥3 months earlier (Table I). The main criterion for patient selection was stable angina pectoris with a positive exercise test result. Patients with Prinzmetal's variant angina, intraventricular conduction disturbances, left ventricular strain pattern, postural or hyperventilation ST changes and those taking drugs known to influence the ST-segment were excluded. Two patients did not complete the studies. One of them had a severe headache that did not allow him to take the drug. The other patient was not present at control examinations 3 weeks later. Therefore, a total of 30 patients were taken into account in the final evaluation. Seven days before Holter recording and stress testing all cardioactive drugs apart from sublingual nitroglycerin, if necessary, had been withdrawn. The studies were performed in a parallel, double-blind manner. At 6 and 7 days after drug withdrawal, 48-hour ambulatory electrocardiographic monitoring was performed followed by a treadmill exercise test. The patients received a placebo or slow-release ISDN in a single dose of 120 mg/day for 3 weeks. Forty-eight-hour electrocardiographic monitoring was repeated at 20 and 21 days of drug or placebo administration. At 21 days exercise testing was also repeated 2 hours after drug ingestion.

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Ambulatory ST-segment recordings were obtained using the digital recorder SEER (Marquette Electronics Inc.). The magnitude of ST-segment depression was assessed from leads CS_2 and CM_5 and alterations were recorded as trends on 2 channels. They were then compared with the electrocardiographic tracing of each ischemic episode. The electrocardiographic strips were then analyzed to find the time of onset and the duration of ST-segment depression for each consecutive episode. Patients kept their diaries, noting the time of onset and duration of painful episodes. On the basis of Holter recordings and patients' notes we identified painful and painless episodes. An episode of ischemia was defined as ≥1.0 mm of horizontal or downsloping ST-segment depression at 80 ms from the J point lasting for 1 minute or more.[13]

A treadmill exercise test (CASE-12, Marquette Electronics Inc.) was performed according to the modified Bruce protocol.[14] The test was interrupted when submaximal heart rate (85% of maximal heart rate) had been achieved or when limiting symptoms had appeared. The magnitude of ST-segment depression was evaluated for each minute of the exercise, immediately and at 2, 4, 6, 8 and 12 minutes after its termination. A significant episode was defined as ≥1.0 mm of ST-segment depression at 80 ms from the J point compared with the rest of the ST-segment level.

Statistical analysis: The differences in between-group results were analyzed using the Mann-Whitney and Wilcoxon tests.

RESULTS

Holter monitoring: Before treatment on the first day of electrocardiographic monitoring 15 patients who received slow-release ISDN had 77 (45%) and 94 (55%) painful and painless episodes of ST-segment depression, respectively; on the second day they had 84 (45%) and 102 (55%) painful and painless episodes, respectively. The total number of painful and painless episodes of ST-segment depression was 357, and all patients experienced >1 episode within 48 hours of Holter monitoring. There were 161 painful (45%) and 194 painless (55%) episodes. The difference in the incidence of both types of episodes between the 2 days is not statistically significant ($p > 0.05$). Lack of significant differences was also seen in the placebo group, in which the subjects experienced 62 painful (42%) and 86 painless (58%) episodes of ST-segment depression on the first day of electrocardiographic monitoring, and 80 painful (45%) and 98 painless (55%) episodes on the second day. The total number of episodes within 48 hours was 326, including 142 painful (44%) and 184 painless (56%) episodes in the placebo group.

At 3 weeks the number of painful and painless episodes of ST-segment depression decreased markedly in the group taking the active drug. Patients who had 48-hour electrocardiographic monitoring exhibited a total of only 43 episodes (23 painful [54%] and 20 painless [46%]). The differences in the incidence of both types of episodes are highly significant in the patients receiving ISDN ($p < 0.001$). In this group 4 patients (27%) did not experience symptomatic episodes on the 21st day of drug therapy. At 3 weeks 48-hour electrocardiographic recording in 3 patients (20%) showed no asymptomatic episodes of ST-segment depression; on the second day of

TABLE 1 Characteristics of Patients

	Total	ISDN Group	Placebo Group
No. of patients	32	16	16
Men	26	13	13
Women	6	3	3
Age range (yr)	39–62	45–62	39–61
Mean age (yr)	51 ± 5.6	52 ± 4.9	50 ± 5.7
Men	51	52	50
Women	51	53	50
Prior MI	25	13	12
Men	22	12	10
Women	3	1	2

Mean age is ± standard deviation.
ISDN = isosorbide dinitrate; MI = myocardial infarction.

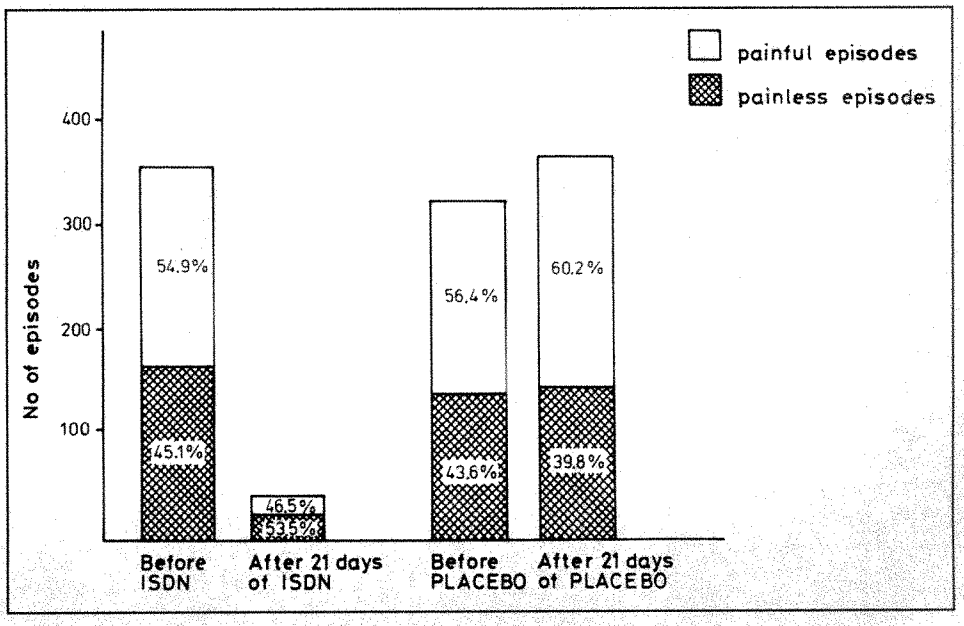


FIGURE 1. Painful and painless episodes of ST-segment depression in patients receiving isosorbide dinitrate (ISDN) or placebo.

TABLE II Changes in Electrocardiogram and Duration of Episodes During Holter Monitoring in Patients Receiving Isosorbide Dinitrate or Placebo

	ISDN Group			Placebo Group		
	Baseline	20th Day	21st Day	Baseline	20th Day	21st Day
Painful episodes						
Duration (s)	797 ± 516	201 ± 224*	122 ± 149*	612 ± 317	708 ± 347	820 ± 598
Painless episodes						
Duration (s)	1,401 ± 1,541	119 ± 103*	104 ± 102*	1,198 ± 1,934	1,337 ± 2,059	1,470 ± 2,328
Painful ST ↓ (mm)	2.7 ± 0.9	1.0 ± 0.6*	0.7 ± 0.7*	2.1 ± 0.8	1.9 ± 0.5	2.1 ± 0.6
Painless ST ↓ (mm)	2.0 ± 1.1	0.7 ± 0.5*	0.7 ± 0.5*	2.1 ± 1.0	2.0 ± 1.0	2.1 ± 1.1

*p <0.001 vs baseline; other changes not significant.
Data are mean ± standard deviation.
ISDN = isosorbide dinitrate; ST ↓ = ST-segment depression.

TABLE III Changes in Initial Blood Pressure, Heart Rate and Work Load During Treadmill Exercise Test in Patients Receiving Isosorbide Dinitrate or Placebo

	ISDN Group		Placebo Group	
	Baseline	21st Day	Baseline	21st Day
Systolic BP (mm Hg)	120 ± 12	113 ± 12*	125 ± 15	129 ± 14†
Diastolic BP (mm Hg)	79 ± 6	75 ± 6*	83 ± 7	82 ± 7
Max. mean HR (beats/min)	124 ± 9	152 ± 12*	129 ± 13	127 ± 16
Max. mean work load (METs)	6 ± 2	10 ± 1*	7 ± 1	6 ± 2

Data are mean ± standard deviation.
*p <0.001 vs baseline; †p <0.05 vs baseline; other changes not significant.
BP = blood pressure; HR = heart rate; ISDN = isosorbide dinitrate.

TABLE IV Changes in Duration of Treadmill Exercise Testing Until Anginal Pain, and ST-Segment Deviations and Changes in ST-Segment Depression During Exercise Testing in Patients Receiving Isosorbide Dinitrate or Placebo

	ISDN Group		Placebo Group	
	Baseline	21st Day	Baseline	21st Day
Test duration until AP (s)	461 ± 128	830 ± 130*	517 ± 130	508 ± 158
Test duration until ST ↓ (s)	442 ± 137	858 ± 110*	515 ± 151	512 ± 159
ST ↓ (mm)	3.0 ± 1.5	1.2 ± 0.6*	2.5 ± 1.5	2.3 ± 1.4†

Data are mean ± standard deviation.
*p <0.001 vs baseline; †p <0.05 vs baseline; other changes not significant.
AP = anginal pain; ISDN = isosorbide dinitrate; ST ↓ = ST segment depression.

monitoring no ST-depression was seen in 7 patients. Such beneficial changes were not observed in patients receiving a placebo. In this group, control 48-hour electrocardiographic recording at 3 weeks showed a total of 372 episodes (148 painful [40%] and 224 painless [60%]) i.e., 46 more episodes than before placebo administration (Figure 1).

The duration of asymptomatic and symptomatic episodes decreased significantly in the active drug group at 3 weeks ($p < 0.001$). No beneficial changes were observed in the placebo group, in which the increase duration of both painful and painless episodes was not significant (Table II).

The magnitude of ST-segment depression also decreased significantly in patients receiving ISDN during both symptomatic and asymptomatic episodes. In the placebo group there were practically no major differences in the magnitude of ST-segment depression during painful and painless episodes before and at 3 weeks of drug administration (Table II). The present study also showed that the majority of asymptomatic episodes occurred between 6 A.M. and 12 P.M. (44% of all asymptomatic episodes). No significant differences were found in the period of occurrence of asymptomatic episodes during placebo or ISDN treatment.

Treadmill exercise stress test: Patients receiving ISDN had a significant decrease in systolic and diastolic blood pressure at 3 weeks ($p < 0.001$). We did not observe a reduction in arterial blood pressure in patients receiving placebo; on the contrary, we found a slight but statistically significant increase in systolic blood pressure at 3 weeks after placebo administration. During the treadmill exercise test, after 3 weeks of ISDN therapy, a significant increase in the attained heart rate was noted, which represented an increase from 74 to 91% of the expected values. The maximal work load increased from 6 to 10 METs at 21 days after drug therapy ($p < 0.001$) (Table III). A mean duration of the treadmill test to the onset of ST-segment depression lengthened significantly at 3 weeks. A similar significant increase was seen in the duration of the treadmill test to angina onset. Mean maximal ST-segment depression also decreased significantly. Such beneficial changes were not observed in patients receiving a placebo (Table IV).

DISCUSSION

Many investigators believe that silent myocardial ischemia is a significant factor influencing prognosis.[15–20] The Framingham study revealed that about half of unrecognized myocardial infarctions were silent, and the rest were so atypical that the diagnosis was not suspected.[15,16] Prognostic significance of silent myocardial ischemia depends on patient selection,[17] with prognosis being worse in high-risk groups.[7] Morbidity and mortality rates are increased in patients after myocardial infarction and with transient ischemia, the bulk of which is asymptomatic.[18–20] There is a gradual tendency to believe that silent myocardial ischemia is associated with a

risk similar to painful episodes of coronary artery disease.[21-23] In this case an initiation of anti-ischemic therapy in patients with silent myocardial ischemia may significantly alter our strategy in the treatment of coronary artery disease. Accordingly, treatment should aim at eliminating or decreasing the number of not only painful but also painless ischemic episodes.[11] The treatment of patients with detected episodes of silent myocardial ischemia may decrease the risk of reinfarction and sudden death, but further controlled studies are required. At present, ambulatory monitoring not only of ventricular ectopic activity but also of asymptomatic ST-segment depressions during normal daily activities is being performed more often.[24,25] With Holter monitoring, both the depression and elevation of ST-segment changes have been found to correlate with other ischemic signs.[13,25,26] Deanfield et al,[13] in analyzing relationships between myocardial uptake of rubidium-82 and electrocardiographic ST-segment changes during bicycle exercise testing in patients with stable angina and in normal subjects, found that ischemic changes in healthy persons were absent in electrocardiographic tracings after exercise, whereas ST-segment depression as well as a decreased uptake of rubidium-82 was noted in a large number of patients with coronary artery disease. This indicates that electrocardiographic ST-segment changes are indicative of myocardial ischemia. A number of studies show that the incidence of painless episodes accompanied by ST-segment depressions may range from 70 to 90%.[10,11,13,25,26]

Our double-blind study indicates beneficial effects of slow-release ISDN in a single dose of 120 mg/day on the incidence of painful and painless episodes of myocardial ischemia manifested by ST-segment depression during 48-hour electrocardiography in patients with stable angina pectoris. Administration of a drug in a single dose may favorably influence the patients' well-being, and it may also be a factor improving the patient-physician relation, so important in chronic therapy. In our study the number of asymptomatic episodes decreased 9 times, whereas the number of painful ST-segment depressions decreased 8 times. ISDN also produced a several-fold decrease in the duration of painful and painless episodes, as well as a significant reduction in the magnitude of symptomatic and asymptomatic ST-segment depressions during Holter monitoring. During ISDN treatment the maximal work load increased by more than 1.5 times. Patients receiving a placebo had no improvement in the number of painful and painless episodes, in their type in the 48-hour electrocardiographic recording, or in the work load during the treadmill exercise test.

Recent studies also show favorable effects of ISDN in patients with silent myocardial ischemia,[4,6,9,27] emphasizing a reduction in the frequency of both painful and painless ischemic episodes. The results of trials with nitrates suggest that medium-sized coronary arteries, such as epicardial arteries, may be particularly susceptible to their influence.[28] Brown[28] found that nitroglycerin and ISDN increase the luminal area of normal coronary arterial segments by an average of 20% and the diameter at the site of stenosis by 29%. They claim that nitrates may not only dilate about 70% of coronary stenosis but also increase coronary collateral flow to the ischemic myocardium, thereby preventing or reversing myocardial ischemia. In recent years Feng et al[30] and others[10,29] have found that nitrates significantly reduce the incidence of silent ischemic episodes.

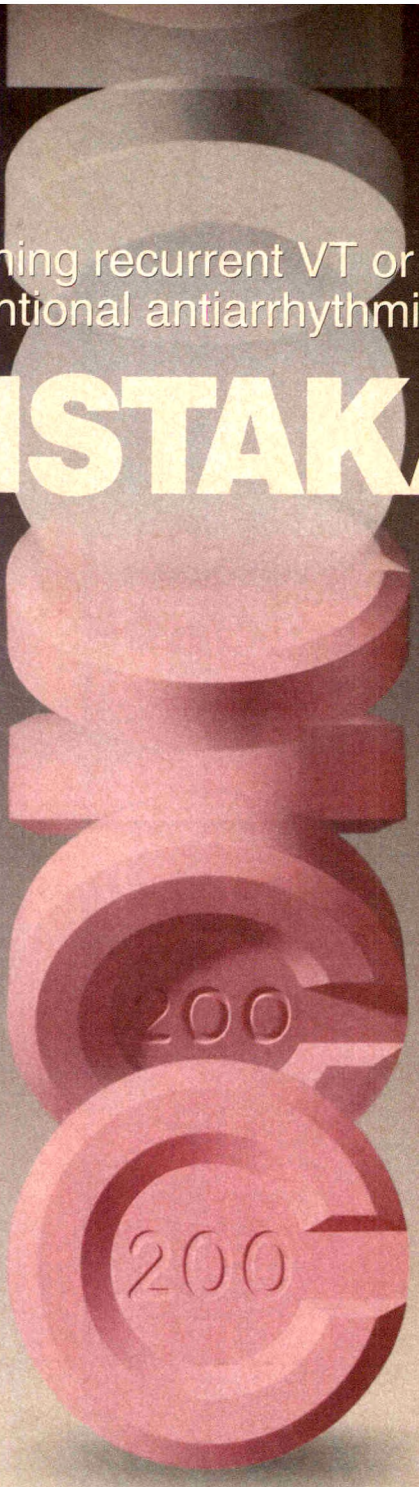
From these and other studies it may be assumed that improved myocardial perfusion resulting from coronary vasodilatation and a simultaneous decrease in myocardial oxygen demand after ISDN significantly attenuate silent myocardial ischemia.

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BRIEF SUMMARY
(See Package Circular for full prescribing information.)

Indications and Usage: Because of life-threatening side effects and substantial management difficulties (See "Warnings" below) use only for treating documented, life-threatening recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia that are unresponsive to documented adequate doses of other antiarrhythmics or when alternative agents are not tolerated.

Controlled trials show no evidence that Cordarone favorably affects survival.

For use only by physicians familiar with and with access to (directly or via referral) all available modalities for treating recurrent life-threatening ventricular arrhythmias, including access to appropriate monitoring facilities and continuous electrocardiographic monitoring and electrophysiologic techniques. Due to the life-threatening nature of the arrhythmias treated, potential interactions with prior therapy, and potential arrhythmia exacerbation, start Cordarone in a hospital setting.

Contraindications: Severe sinus-node dysfunction, with marked sinus bradycardia; 2nd- and 3rd-degree atrioventricular (AV) block; episodes of bradycardia which cause syncope (except when used with a pacemaker); known hypersensitivity to the drug.

Warnings: Cordarone is intended for use only in patients with the indicated life-threatening arrhythmias because its use is accompanied by substantial toxicity.

Cordarone has several potentially fatal toxicities, the most important of which is pulmonary toxicity (hypersensitivity pneumonitis or interstitial/ alveolar pneumonitis) that has resulted in clinically manifest disease at rates as high as 10 to 17% in some series of patients with ventricular arrhythmias given doses around 400 mg/day, and as abnormal diffusion capacity without symptoms in a much higher percentage of patients. Pulmonary toxicity has been fatal about 10% of the time. Liver injury is common with Cordarone, but is usually mild and evidenced only by abnormal liver enzymes. Overt liver disease can occur, however, and has been fatal in a few cases. Like other antiarrhythmics, Cordarone can exacerbate the arrhythmia, e.g., by making the arrhythmia less well tolerated or more difficult to reverse. This has occurred in 2-5% of patients in various series, and significant heart block or sinus bradycardia has been seen in 2-5%. All of these events should be manageable in the proper clinical setting in most cases. Although the frequency of such proarrhythmic events does not appear greater with Cordarone than with many other agents used in this population, the effects are prolonged when they occur.

Even in patients at high risk of arrhythmic death, in whom the toxicity of Cordarone is an acceptable risk, Cordarone poses major management problems that could be life-threatening in a population at risk of sudden death, so that every effort should be made to utilize alternative agents first.

The difficulty of using Cordarone effectively and safely itself poses a significant risk to patients. Patients with the indicated arrhythmias must be hospitalized while the loading dose of Cordarone is given, and a response generally requires at least one week, usually two or more. Because absorption and elimination are variable, maintenance-dose selection is difficult, and it is not unusual to require dosage decrease or discontinuation of treatment. In a retrospective survey of 192 patients with ventricular tachyarrhythmias, 84 required dose reduction and 18 required at least temporary discontinuation because of adverse effects, and several series have reported 15 to 20% overall frequencies of discontinuation due to adverse reactions. The time at which a previously controlled life-threatening arrhythmia will recur after discontinuation or dose adjustment is unpredictable, ranging from weeks to months. The patient is obviously at great risk during this time and may need prolonged hospitalization. Attempts to substitute other antiarrhythmic agents when Cordarone must be stopped will be made difficult by the gradually, but unpredictably, changing amiodarone body burden. A similar problem exists when Cordarone is not effective; it still poses the risk of an interaction with whatever subsequent treatment is tried.

PULMONARY TOXICITY: Cordarone may cause a syndrome of cough and progressive dyspnea with functional, radiographic, gallium-scan and pathological data consistent with pulmonary toxicity; frequency usually varies from 2-7%, but can be as high as 10-17%. Thus, at start of therapy, perform baseline chest x-ray and pulmonary-function tests, including diffusion capacity. Repeat history, physical exam (PE), and chest x-ray every 3-6 months.

Preexisting pulmonary disease does not appear to increase risk of toxicity; however, prognosis is poorer if pulmonary toxicity develops.

Cordarone-induced pulmonary toxicity seems to result from indirect (hypersensitivity pneumonitis) or direct (interstitial/alveolar pneumonitis) toxicity.

Hypersensitivity pneumonitis usually appears early in therapy; rechallenge results in a more rapid and severe recurrence. Bronchoalveolar lavage is procedure of choice to confirm diagnosis, made when a T suppressor/cytotoxic (CD8 - positive) lymphocytosis noted. Treat with steroids and stop Cordarone.

Interstitial/alveolar pneumonitis characterized by diffuse alveolar damage, interstitial pneumonitis or fibrosis in lung biopsies. Phospholipidosis (foamy cells, foamy macrophages) is present in most cases of Cordarone-induced pulmonary toxicity; however, this also occurs in approximately 50% of all Cordarone patients. Use these cells as therapy markers, not evidence of toxicity. If interstitial/alveolar pneumonitis is diagnosed, reduce dose or, preferably, withdraw Cordarone, especially if other acceptable antiarrhythmics are available. Where these measures were instituted, symptoms usually decreased in the first week; most clinical improvement was in first 2-3 weeks. Chest X-ray changes usually resolve in 2-4 months. Some experts feel steroids may be helpful. Prednisone (40-60 mg/day) or equivalent doses of other steroids have been used and tapered over several weeks. At times rechallenge at a lower dose will not result in return of toxicity. Reports suggest lower loading and maintenance doses are associated with a lower incidence of pulmonary toxicity.

In Cordarone patients, any new respiratory symptoms suggest a possibility of pulmonary toxicity; repeat and evaluate history, PE, chest X-ray, and pulmonary-function tests (with diffusion capacity). A 15% decrease in diffusion capacity has a high sensitivity but only a moderate specificity for pulmonary toxicity; as decreases in diffusion capacity approach 30%, sensitivity decreases but specificity increases. A diagnostic gallium scan may also be performed.

Fatalities from pulmonary toxicity occur in about 10% of cases. However, when life-threatening arrhythmias exist, stop Cordarone (amiodarone HCl) cautiously if drug-induced pulmonary toxicity is suspected. As the most common cause of death in these patients is sudden cardiac death, first rule out other causes of respiratory impairment. Bronchoalveolar lavage or lung biopsy may be necessary to confirm the diagnosis, especially when there is no acceptable alternative therapy.

If hypersensitivity pneumonitis is diagnosed, stop Cordarone and treat with steroids. If Cordarone-induced interstitial/alveolar pneumonitis is diagnosed, start steroids and, preferably, stop Cordarone or, minimally, reduce the dose. Some cases may resolve after dose reduction and steroid use. Sometimes, rechallenge at lower doses did not result in return of interstitial/alveolar pneumonitis; however, pulmonary lesions are irreversible in some.

WORSENED ARRHYTHMIA: Cordarone may cause serious exacerbation of a presenting arrhythmia, possibly enhanced by concomitant antiarrhythmic therapy. Exacerbation (about 2-5% in most series), includes new ventricular fibrillation, incessant ventricular tachycardia, increased resistance to cardioversion, and Torsade de Pointes. Cordarone has caused symptomatic bradycardia or sinus arrest with suppression of escape foci in 2-4% of patients.

LIVER INJURY: Increased hepatic enzymes, mostly asymptomatic, are seen frequently. Consider discontinuation or dose reduction if increase exceeds 3 times normal, or doubles in patient with elevated baseline. Rarely, hepatic failure has been fatal.

PREGNANCY — PREGNANCY CATEGORY D: Cordarone is embryotoxic (increased fetal resorption and growth retardation) in rats at 18 times the maximum recommended oral maintenance dose. Similar results are seen in one mice strain at about 1/2 the maximum recommended maintenance dose or higher, but not in a second strain nor rabbits at doses up to 9 times the maximum recommended maintenance dose.

Neonatal hypo- or hyperthyroidism: In utero exposure can cause fetal harm. There are some reports of congenital goiter/ hypothyroidism and hyperthyroidism. If used anytime during pregnancy apprise patient of potential fetal hazard. In general, use during pregnancy only if potential benefit to the mother justifies unknown fetal risk.

Precautions

CORNEAL MICRODEPOSITS; IMPAIRMENT OF VISION: Corneal microdeposits appear in a majority of adults on Cordarone. Usually discernible only by slit-lamp, up to 10% of patients have symptoms like visual halos or blurred vision. Microdeposits are reversible if dose reduced or treatment stopped; if asymptomatic, no need to reduce dose or stop drug.

PHOTOSENSITIVITY: Seen in about 10% of patients; sun-barrier creams or protective clothing may afford some protection. On long-term therapy, may have a blue-gray skin discoloration of exposed skin. Fair complexion or excess sun exposure may increase risk; also may be related to cumulative dose and therapy duration.

THYROID ABNORMALITIES: Cordarone inhibits conversion of thyroxine (T_4) to triiodothyronine (T_3) and may cause increased thyroxine, decreased T_3, and increased levels of inactive reverse T_3 (rT_3) in clinically euthyroid patients. Due to its release of inorganic iodine, or perhaps other reasons, Cordarone can cause either hypo- or hyperthyroidism. Monitor thyroid function before treatment and periodically thereafter, particularly in the elderly and those with history of thyroid nodules, goiter, or other thyroid dysfunction. Due to slow elimination of Cordarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for weeks or months after withdrawal.

Hypothyroidism occurred in 2-4% of patients in most series, but in 8-10% in some. To treat, reduce Cordarone dose and/or give thyroid hormone supplement. Individualize therapy; may need to stop Cordarone.

Hyperthyroidism occurs in about 2% of patients; incidence may be higher with prior inadequate dietary iodine intake. Cordarone-induced hyperthyroidism is usually a greater hazard than hypothyroidism due to possible arrhythmia breakthrough or aggravation. IF ANY NEW SIGNS OF ARRHYTHMIA APPEAR, THE POSSIBILITY OF HYPERTHYROIDISM SHOULD BE CONSIDERED. Flat TSH response to TRH is confirmatory. Since arrhythmia breakthroughs may accompany Cordarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or Cordarone withdrawal. Antithyroid drugs, β-blockers and/or temporary steroid therapy may be needed. (See full prescribing information for additional information regarding treatment).

SURGERY: *Hypotension Posthypass:* Rarely, hypotension is seen on cessation of cardiopulmonary bypass during open-heart surgery in Cordarone patients; relationship to Cordarone is unknown.

Adult Respiratory Distress Syndrome (ARDS): Rarely, ARDS occurs in Cordarone patients after surgery. Patients usually respond to vigorous respiratory therapy; rarely, the outcome is fatal. The mechanism may be generation of superoxide radicals during oxygenation; therefore, keep operative FiO_2 as close to room air as possible.

LABORATORY TESTS: Elevated liver enzymes (SGOT and SGPT) can occur; monitor closely if high maintenance doses used. Consider dose reduction or stopping therapy if significant elevations persist or hepatomegaly occurs.

Thyroid-function tests (increased T_4 and reverse T_3, and decreased T_3) may be altered; despite these changes, most patients remain clinically euthyroid.

DRUG INTERACTIONS: Few drug-drug interactions have been explored formally but most have shown an interaction. Thus, anticipate other interactions, especially drugs with potentially serious toxicity, like other antiarrhythmics. With its long, variable half-life, a potential for interaction also exists with drugs given after stopping Cordarone.

Digitalis: Serum digoxin increases (by up to 70%) and may reach toxic levels; onset is about 1 day. **On initiation of Cordarone, review need for digitalis and reduce its dose by about 50% or stop it.** If digitalis continued, monitor serum levels closely and observe for toxicity. Precautions probably also apply to digitoxin.

Anticoagulants: Potentiation of warfarin-type anticoagulant response is almost always seen and can result in serious or fatal bleeding. Prothrombin time may increase by 100%; onset is 3 to 4 days. **Reduce anticoagulant dose by 1/3 to 1/2, and monitor prothrombin times closely.**

Antiarrhythmic Agents: Although they have been used concurrently with Cordarone, steady-state levels of quinidine, procainamide, and phenytoin may increase during such combined therapy. Quinidine serum concentrations may increase by 33% within 2 days. Procainamide serum concentrations may increase by 55% (n-acetyl procainamide by 33%) in < 7 days. In general, reserve such combinations for patients with life-threatening ventricular arrhythmias incompletely responsive to a single agent, or incompletely responsive to Cordarone (amiodarone HCl), and start any added antiarrhythmic at a lower than usual dose with careful monitoring. During transfer to Cordarone, reduce dose of previous agents 30-50% several days after adding Cordarone; when arrhythmia suppression should be starting. After Cordarone effects are established, discontinue other antiarrhythmics if possible. If treatment is maintained, continue monitoring carefully for adverse effects, especially conduction disturbances and exacerbation of tachyarrhythmias. In Cordarone patients requiring additional antiarrhythmic therapy, initial dose of such agents should be approximately 1/2 of the usual dose.

Use Cordarone cautiously with β-blockers or calcium antagonists as bradycardia, sinus arrest, and AV block may be potentiated; if necessary, Cordarone can continue after pacemaker insertion in patients with severe bradycardia or sinus arrest.

ELECTROLYTE DISTURBANCES: May be ineffective or arrhythmogenic if hypokalemia is present; correct any potassium or magnesium deficiency before starting drug.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Fertility reduced in male and female rats at 8 x the highest recommended human maintenance dose. Cordarone caused a statistically significant, dose-related increase in thyroid tumors in rats. Incidence greater than control even at lowest dose tested, i.e., about 1/2 the highest recommended human maintenance dose. Mutagenicity studies were negative.

PREGNANCY: PREGNANCY CATEGORY D — See **Warnings.**

LABOR AND DELIVERY: Occurrence of adverse effects during labor or delivery is unknown. Preclinical studies in rodents have shown no effect on gestation duration or parturition.

NURSING MOTHERS: Cordarone is excreted in human milk; breast-feeding may expose nursing infants to a significant drug dose. Nursing offspring of lactating rats given Cordarone were less viable and had reduced body-weight gains. Advise mothers to discontinue nursing before taking.

PEDIATRIC USE: Safety and effectiveness have not been established.

Adverse Reactions: Adverse effects are very common (about 3/4 of all patients) with doses of 400 mg/day or more, and cause 7-18% to discontinue. The most serious are pulmonary toxicity, arrhythmia exacerbation, and rare serious liver injury (see "**Warnings**"), but other adverse effects constitute important problems. They are often reversible by reducing dose and virtually always reversible by stopping Cordarone. Most adverse effects appear more frequent with continued treatment beyond 6 months; rates appear relatively constant beyond one year. Neurologic problems, including malaise and fatigue, tremor and involuntary movements, poor coordination and gait, and peripheral neuropathy are common (20-40% of patients); these may respond to dose reduction, rarely need to stop therapy.

Gastrointestinal (GI) complaints, commonly seen with high doses (i.e., loading dose), usually respond to dose reduction or divided doses; rarely need to stop drug.

Asymptomatic corneal microdeposits. See **Precautions** and full prescribing information.

Photosensitivity. See **Precautions** and full prescribing information.

Cardiovascular adverse reactions, other than arrhythmia exacerbation, include the uncommon occurrence of congestive heart failure (3%) and bradycardia. Bradycardia usually responds to dose reduction but may require a pacemaker. CHF rarely requires stopping drug. Cardiac conduction abnormalities occur infrequently and are reversible upon stopping drug.

The following side-effect rates are based on a retrospective study of 241 patients treated for 2 to 1,515 days (mean 441.3 days).

Each reported in 10-33% of patients: GI--Nausea and vomiting.

Each reported in 4-9% of patients: Dermatologic--Solar dermatitis/photosensitivity; Neurologic--Malaise and fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias; GI--Constipation, anorexia; Ophthalmologic--Visual disturbances; Hepatic--Abnormal liver-function tests; Respiratory--Pulmonary inflammation or fibrosis.

Each reported in 1-3% of patients: Thyroid--Hypo- or hyperthyroidism; Neurologic--Decreased libido, insomnia, headache, sleep disturbances; Cardiovascular--CHF, cardiac arrhythmias, SA node dysfunction; GI--Abdominal pain; Hepatic--Nonspecific hepatic disorders; Other--Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities.

Each reported in < 1% of patients: Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, and cardiac conduction abnormalities. Rarely hepatitis, cholestatic hepatitis, cirrhosis, optic neuritis, epididymitis, vasculitis, pseudotumor cerebri, and thrombocytopenia.

Adverse reactions most frequently requiring Cordarone discontinuation include pulmonary infiltrates or fibrosis, paroxysmal ventricular tachycardia, CHF, and elevated liver enzymes. Symptoms causing discontinuation less often include visual disturbances, solar dermatitis, blue skin discoloration, hyper- or hypothyroidism.

Overdosage: The few reports of Cordarone overdose, in which 3 to 8 grams were taken, resulted in no deaths or permanent sequelae. Animal studies indicate that Cordarone has a high oral LD_{50} (>3,000 mg/kg).

Along with general supportive measures, monitor patient's cardiac rhythm and blood pressure; if bradycardia ensues, may use a β-adrenergic agonist or pacemaker. Use positive inotropic and/or vasopressor agents to treat hypotension with inadequate tissue perfusion. Neither Cordarone nor its metabolite is dialyzable.

Dosage and Administration: See full prescribing information.

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Comparison of Results of Percutaneous Transluminal Coronary Angioplasty With and Without Selective Requirement of Surgical Standby

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To determine the outcome of percutaneous transluminal coronary angioplasty (PTCA) with the use of 2 different strategies of surgical coverage, the results of 1,283 consecutive PTCAs were analyzed. In 269 procedures (21%) (patients considered at high risk should acute vessel closure occur — standby group) the operating room and the surgical team were ready for an immediate intervention. In the remaining 1,014 procedures (79%) (backup group), although the surgical team was "in house," they were not necessarily ready for an immediate intervention. Mean age of the population was 58 ± 10 years and 84% of patients were men. Coronary risk factors, medical treatment, clinical indication for PTCA, previous coronary surgery and left ventricular ejection fraction were similar in both groups. Dilatation was more frequently multiple (23 vs 16%, p <0.05), or performed in the left anterior descending coronary artery (71 vs 46%, p <0.001), in bypass grafts (4 vs 2%, p <0.02), in proximal coronary segments (72 vs 57%, p <0.001) or in lesions at bifurcation (35 vs 28%, p <0.02) in the standby than in the backup group, respectively. PTCAs were less frequently performed during the same diagnostic procedure (15 vs 34%, p <0.001) in the standby group. Angiographic success was obtained in 91 and 92% of the attempted lesions and PTCA success in 89 and 88% of the procedures in the standby and backup groups, respectively. The incidence of death (1 vs 0.7%), acute myocardial infarction (2.9 vs 2.7%) and emergency surgery (0.7 vs 0.1%) was also similar in both groups. Our results suggest that (1) PTCA is a safe procedure with a relatively low incidence of complications, independent of the surgical coverage used; (2) a rigorous surgical standby is not necessary during all PTCA procedures; and (3) criteria for a better selection of high-risk patients who will require a rigorous surgical coverage are still urgently needed.

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There are specific emergency situations during percutaneous transluminal coronary angioplasty (PTCA) in which surgery provides an expeditious method to solve complications. For this reason an experienced cardiovascular surgical team should always be available for emergency surgery when PTCA procedures are being performed.[1] However, the precise arrangement for surgical standby varies from institution to institution. After PTCA, an incidence of 2 to 11% of acute coronary vessel closure has been reported.[2–6] Acute coronary vessel closure does not always imply a new myocardial infarction. Patients with acute closure during PTCA usually are considered candidates for emergency surgical revascularization in order to prevent acute myocardial ischemia and ongoing myocardial infarction. Nevertheless, previous studies reported that 33 to 71% of patients who underwent emergency surgery developed a new myocardial infarction and 3 to 6% of them died during the perioperative period.[3,7,8] In addition, a repeat dilatation of the acutely closed vessel may be attempted as a conservative alternative to emergency bypass surgery.[4–6] For this reason and because of the suboptimal results obtained with emergency coronary surgery after PTCA-related complications, we designed the present study to evaluate the impact of 2 strategies of surgical coverage, namely a "rigorous surgical standby" and a "surgical backup" ("in house" surgical team, but not necessarily ready to operate immediately), in the short-term results of PTCA.

METHODS

Between January 1986 and December 1990, a total of 1,283 consecutive PTCAs were performed at our institution. In 269 PTCAs (21%) (334 lesions, 229 patients) a rigorous standby surgery was organized (standby group). In the remaining 1,014 PTCAs (79%) (1,204 lesions, 841 patients) (backup group) such type of surgical coverage was not required, although cardiac surgery was still available "on site." PTCAs were performed using steerable guidewire coronary angioplasty systems with a conventional coaxial or monorail technique. During the last 287 procedures of this series, the Palmaz-Schatz coronary stent was available and coronary stenting was considered in patients with suboptimal result, large subocclusive dissection or acute vessel closure during PTCA.

Definitions: Angina was considered unstable if at rest, recent onset (<1 month), after infarction or pro-

TABLE I Demographic Data

	Groups	
	Standby	Backup
No. of procedures/pts.	269/229	1,014/841
Age (yr)	57 ± 9	59 ± 11
Men/women	169/60	699/142
Coronary risk factors		
Hypertension	119 (44%)	453 (45%)
Diabetes	58 (22%)	173 (17%)
Hypercholesterolemia	95 (35%)	415 (41%)
Smokers	186 (69%)	698 (69%)
Family history	63 (23%)	222 (22%)
Prior myocardial infarction	112 (42%)	454 (45%)
Prior coronary surgery	21 (8%)	63 (6%)
Prior cardiac failure	15 (6%)	30 (3%)
Treatment before PTCA		
Nitrates	213 (79%)	848 (84%)
β blockers	108 (40%)	395 (39%)
Calcium antagonists	221 (82%)	795 (79%)
Aspirin	191 (71%)	729 (72%)
Heparin	34 (13%)	127 (12%)

PTCA = percutaneous transluminal coronary angioplasty.

gressive despite adequate medical treatment. Coronary artery disease was considered multivessel if stenosis >50%, by visual assessment, was present in ≥2 major coronary arteries. Only severe stenosis (≥75%) was considered for dilatation. Angiographic success was defined if luminal narrowing was reduced >20% and residual stenosis <50%.[1] PTCA procedures were considered successful when (1) angiographic success was achieved; (2) no major complication (death, acute myocardial infarction, cardiac surgery) occurred during hospitalization; and (3) there was no evidence of vessel closure during hospitalization. In patients undergoing multivessel dilatation, the PTCA procedure was considered successful if, at least the "culprit" lesion was successfully dilated and there was absence of major complications.[9] Acute vessel occlusion was considered as "early closure" when it occurred during the procedure, before the patient had left the catheterization room, and as "late closure" when a vessel, initially dilated with success, had acute occlusion after the patient had left the catheterization room, but during hospitalization.

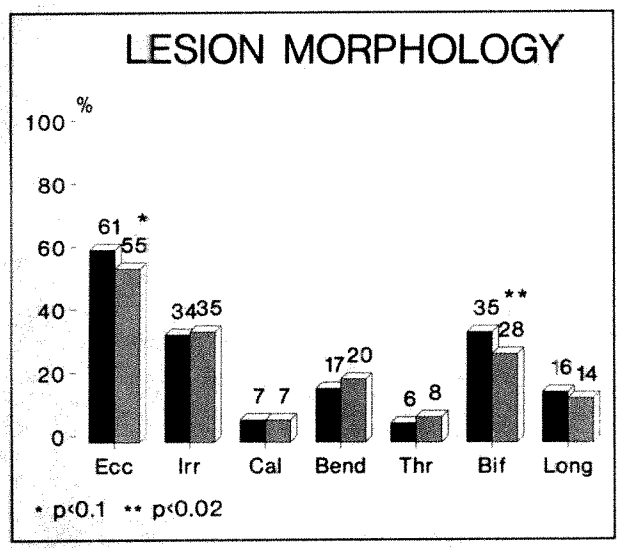


FIGURE 1. ***Solid bar,*** **standby group;** ***slashed bar,*** **backup group. Bend = at bend point ≥45°; Bif = at bifurcation; Cal = calcified; Ecc = eccentric; Irr = irregular; Long = lesion length ≥10 mm; Thr = thrombus.**

Surgical coverage was considered as standby if the surgical team and the operating room were ready for an emergency intervention to be started immediately. Standby surgery was required for patients who were potential surgical candidates and in whom the eventual closure of the attempted vessel was considered to be life-threatening. In the remaining patients, urgent surgery was still possible because the surgical team was in-house, but not necessarily ready to operate immediately (surgical backup group). General guidelines to exclude patients for rigorous surgical coverage were: patients not willing to be operated on, coronary anatomy not considered suitable for surgical revascularization, a concomitant severe noncardiac disease, a prior myocardial infarction in the myocardium supplied by the vessel to be dilated, or dilatation of vessels with chronic total occlusions. Nevertheless, the decision of the kind of surgical coverage required during PTCA was eventually made, on an individual basis, by the cardiologist performing the procedure, taking clinical and angiographic factors into consideration.

Data management and analysis: Data were prospectively entered into a database specially designed for PTCA (Angiosystem-Cormedica™) installed on an IBM computer. Discontinuous variables were analyzed as percentages and continuous variables as mean ± standard deviation, and compared by the chi-square and Student's *t* test, respectively. Differences were considered statistically significant at $p < 0.05$. A logistic regression analysis was performed using computer software (SPSS/PC + Advanced Statistics™, V2.0) to determine independent correlates of acute vessel closure.

RESULTS

Age, sex, coronary risk factors and patient's medication were similar in both groups (Table I). Indication for PTCA was also similar in both groups: unstable angina in 188 (70%) versus 681 (67%) (p = not significant [NS]), stable angina in 54 (20%) versus 205 (20%) (p = NS), acute myocardial infarction in 6 (2%) versus 40 (4%), and silent ischemia in 21 (8%) versus 88 (9%) in the standby and backup groups, respectively. Baseline lesion morphologic features are shown in Figure 1. Table II summarizes the angiographic findings. A previous inferior myocardial infarction was present in 221 patients (34 in the standby and 187 in the backup groups). The attempted lesion was located in the left anterior descending coronary artery in 13 of these patients (38%) with a previous inferior myocardial infarction in the standby group and in 30 patients (16%) in the backup group ($p < 0.01$).

Procedural data: Standby group patients underwent multiple dilatation more frequently (>1 lesion or >1 vessel, or both) and PTCA during the same angiographic diagnostic procedure less frequently than in the backup group patients. Angiographic and PTCA success rates were similar in both groups (Table III). In cases of

TABLE II Angiographic Findings

	Groups		
	Standby	Backup	
No. of arteries narrowed	334	1,204	
Native coronary artery	321 (96%)	1,179 (98%)	NS
Grafts	13 (4%)	25 (2%)	<0.02
Native lesion location			
Left anterior descending artery	227 (71%)	539 (46%)	<0.001
Circumflex artery	42 (13%)	266 (22%)	<0.01
Right coronary artery	52 (16%)	374 (32%)	<0.001
Segment location			
Proximal	240 (72%)	687 (57%)	<0.001
Middle/distal	94 (28%)	517 (43%)	<0.001
Stenosis before PTCA	87 ± 8%	88 ± 26%	NS
Stenosis after PTCA	28 ± 23%	26 ± 22%	NS
1-vessel disease	150 (56%)	592 (58%)	NS
Totally occluded vessels	20 (6%)	97 (8%)	NS
Collateral circulation	68 (20%)	218 (18%)	NS
LVEF	65 ± 11	64 ± 13	NS
LVEF < 50%	23 (12%)	121 (16%)	NS

LVEF = left ventricular ejection fraction; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

TABLE III Procedural Data

	Groups		
	Standby	Backup	
No. of procedures/narrowings	269/334	1,014/1,204	
Multiple dilatation	61 (23%)	163 (16%)	p <0.02
PTCA during diagnosis	40 (15%)	343 (34%)	p <0.001
Angiographic success	304 (91%)	1,104 (92%)	NS
PTCA success	240 (89%)	895 (88%)	NS

NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

multiple dilatation, a mean of 2.3 ± 0.6 versus 2.3 ± 0.7 lesions, per procedure, were attempted in the standby and backup groups, respectively. Dilatation was not successful in 9% of lesions (30 of 334) in the standby group versus 8% (100 of 1,204) in the backup group.

Complications — early and late acute vessel closure: A total of 68 major complications occurred (5.3% of total PTCA or 6.3% of patients), with no differences between the standby and backup groups: acute myocardial infarction (8 cases [2.9%] vs 28 [2.7%]), emergency surgery (2 cases [0.7%] vs 1 [0.1%]), elective surgery (6 cases [2.2%] vs 12 [1.2%]) or death (3 cases [1%] vs 8 [0.7%]).

Of the 8 patients who died in the backup group, 3 were elderly patients (>75 years) who refused surgical revascularization before PTCA; 1 patient, with a metallic prosthesis (aortic position), died during an unsuccessful rescue PTCA for a left main emboli that caused an acute myocardial infarction complicated with cardiogenic shock; 1 patient died of a gastrointestinal hemorrhage 36 hours after PTCA; 1 patient died of an undiagnosed subacute pericardial tamponade 6 hours after PTCA; 1 additional patient died suddenly 8 days after PTCA; and the last patient died during an emergency coronary angiography performed because of an acute ischemic event 16 hours after PTCA, with demonstration of occlusion of the left circumflex artery (dilated artery) and a subocclusive thrombus in the left anterior descending coronary artery (previously normal) without time to be transferred to the operating room. Two patients died during cardiac surgery, 1 from the standby group (emergency surgery for right coronary artery dissection, despite an ischemic time <90 minutes) and 1 from the backup group (elective surgery for left anterior descending coronary artery dissection complicated with non-Q-wave myocardial infarction).

A total of 41 lesions (2.7%) had in-hospital acute occlusion (13 [32%] early closure and 28 [68%] late closure). Of the 13 lesions with early closure, 6 (1.8%) were from the standby group and 7 (0.6%) from the backup group (p <0.1). By univariate analysis, none of the several clinical and angiographic baseline characteristics correlated with early closure during PTCA. Of the 28 lesions that had late closure, 5 were from the standby group and 23 from the backup group (p = NS). This represents 1.6 versus 2% of the lesions initially dilated with success in both groups. The in-hospital course of the 41 lesions (41 patients) with acute vessel closure is represented in Figure 2. Of the 41 lesions with acute occlusion, 26 were treated with a repeat PTCA and angiographic success was achieved in 13 (50%). However, 4 of these patients eventually developed an acute myocardial infarction. Thus, PTCA success was achieved in 9 of 26 patients (35%). Seven of the 41 patients (17%) who experienced acute vessel closure (early or late) died during hospitalization (2 patients during surgery, 1 after thrombolytic therapy, 2 elderly patients treated conventionally who refused surgery, 1 from a stroke 36 hours after a PTCA with stent deployment and 1 patient of refractory ventricular fibrillation while he was waiting for elective surgery).

PTCA performed in the first 24 hours of an acute myocardial infarction (3 of 46 lesions [7%] vs 25 of 1,492 lesions [1.6%] [p <0.05]) and dilatation of totally occluded lesions (5 of 107 lesions [5%] vs 23 of 1,431 lesions [1.6%] [p <0.02]) were associated with late acute closure on univariate analysis, but that association disappeared on multivariate analysis.

Vessel patency (after suboptimal result, or large or subocclusive dissection) was achieved with a successful Palmaz-Schatz stent deployment in 22 lesions (3 from the standby and 19 from the backup groups).

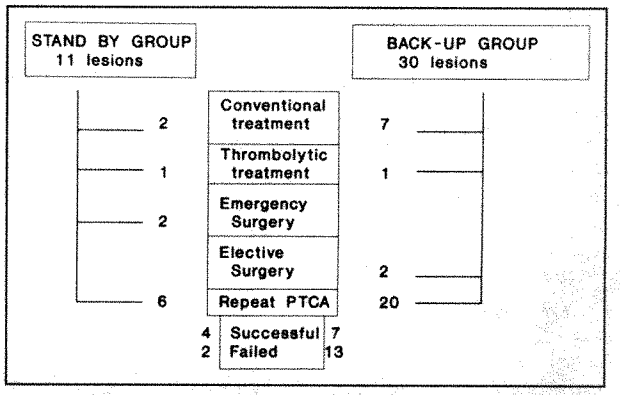


FIGURE 2. In-hospital course of the 41 lesions (41 patients) with acute vessel closure. PTCA = percutaneous transluminal coronary angioplasty.

DISCUSSION

The presence of a rigorous surgical coverage was considered mandatory during the initial stages of PTCA technique.[1,2] The reason for this policy was an incidence of acute myocardial infarction of 4.9% and requirement of emergency coronary surgery in 5.8% of patients during PTCA.[2,3,7,8] At present, even with more complex lesions attempted, the PTCA success rate is 90% and the incidence of emergency surgery has decreased to 3.5%[10] and to 1.6 to 2.7% in recent series.[11,12] Several reasons have contributed to this fact: (1) Emergency revascularization surgery is not always the best approach to the problem of acute closure during or after PTCA. The results reported in the largest series of emergency surgery after complicated PTCA demonstrated a perioperative acute myocardial infarction rate from 21 to 71%, and an in-hospital incidence of death of 1 to 12%.[3,7,8,13-19] (2) Nowadays, many periprocedural coronary occlusions can be successfully managed with repeat balloon dilatation, with a mortality rate ranging from 0 to 20%,[2,4-6,20] comparable to the mortality rate of emergency surgery. (3) In addition, other alternative therapeutic techniques (autoperfusion catheters, laser, stents, atherectomy devices)[21,22] may improve patients' tolerance to ischemia or to PTCA results, or both, and may be eventually used to treat PTCA complications in an attempt to reduce the need for emergency surgery. (4) The dramatic increase in the number of PTCAs in the last few years has made the need for a procedural risk stratification mandatory; therefore, different kinds of surgical coverage might be required. Only 1 preliminary study by Muller et al[23] has been reported on this issue. In this study, high-risk patients (according to the size of the infarction expected in the event of acute vessel closure) on whom surgical coverage was required were characterized by better ejection fraction, more frequent left anterior descending coronary artery dilatation, less collateralized vessels and a lower incidence of prior infarction. No patient died in this high-risk group versus 7 patients (1.2%) in the low-risk group (surgical coverage not required in advance), 8% of patients had a new myocardial infarction versus 5%, and 3.5% required emergency surgery versus 0.3% in both groups, respectively.[23] In our study, patients who underwent dilatation of the proximal segment of the left anterior descending coronary artery (in particular those with a previous inferior myocardial infarction), dilatation of lesions at a bifurcation point, those undergoing multiple dilatation, or patients on whom dilatation of lesions in bypass grafts was planned, were preferably considered to be high risk. They may probably require a rigorous standby surgery. Despite this, and in agreement with others,[11,12] major complication rate (death, acute myocardial infarction, cardiac surgery) was relatively low in our series (5.3% of total PTCAs) and was not significantly different in the groups considered high- or low-risk (7 vs 5%, respectively). With such unpredictable and low complication rates, very large series would be required to demonstrate the usefulness of any interventional approach (e.g., full standby surgery). Nevertheless, patients with unstable angina (according to rather restrictive definition)[2,24,25] and unfavorable morphologic characteristics of the lesion (type B2 or C, eccentric) have been associated with a higher risk of complications.[4,5,9,12]

The report of Richardson et al[26] and Shaw[27] demonstrated that with careful selection of patients (1-vessel disease and normal left ventricular function), PTCA might even be safely performed in a hospital with "off site" cardiac surgery.

In our experience, the low rate of patients who were referred for emergency surgery could be related to (1) the deployment of coronary stents in cases of periprocedural dissection or acute occlusion, and (2) our policy of managing PTCA-related complications in a conservative way, with preference of repeat PTCA and elective rather than emergency surgery. This approach may be the treatment of choice in most patients with acute angioplasty complications for several reasons: (1) The mortality rate was similar in the backup group compared with the standby group. (2) There were no deaths in the backup group, which might be attributed to the delay in surgical revascularization. (3) In our series, up to 35% of vessels attempted after acute closure were successfully reopened by repeat PTCA. (4) Only 4 of the 41 patients (10%) with evidence of acute vessel closure who were managed by repeat PTCA, thrombolytic therapy or conventional methods died of cardiac causes during hospitalization. This death incidence is similar to that reported after emergency surgery. Finally, as a socioeconomic consideration, the cost of a rigorous standby surgical team has been estimated at $630.00 per procedure and the number of hours a complete surgical team should spend in a "non-productive" activity, at 38 hours/month.[28] Moreover, as Richardson et al[26] suggested, a rigorous surgical standby team may also increase the already long waiting list for surgery that exists in many countries with National Public Health Services. For these reasons, we believe that a full surgical standby team should be reserved for a limited number of high-risk patients.

Study limitations: The major limitation of this study is that it is nonrandomized. Nevertheless, randomization of patients considered to be at high risk presents serious ethical limitations. The few end point events observed for the entire study group may justify that statistical analysis could not detect any differences that may exist (type 2 error). A strict prospective study rather than a retrospective analysis of prospectively collected data would have been preferable. Patients were assigned to the standby or backup groups according to the previously defined criteria, but the cardiologist performing the procedure always made the final decision. Accordingly, the decision was performed on an individual basis, and some degree of subjectivity usually involved the selection of the kind of surgical coverage used. However, marked heterogenicity in the extent of jeopardized myocardium implies that stratification of risk cannot be performed from angiographic information alone.[29]

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Frequency and Prognostic Significance of Silent Coronary Artery Disease in Patients with Cerebral Ischemia Undergoing Carotid Endarterectomy

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To evaluate the prevalence and prognostic role of silent coronary artery disease (CAD) in patients with symptomatic high-grade carotid stenosis (70 to 99%) undergoing carotid endarterectomy, and with neither history nor symptoms of CAD, 106 patients (76 men, 30 women, mean age 58.7 years [range 42 to 71]) with recent cerebral ischemia were prospectively studied. Patients were stratified as to the presence (n = 27, 25%) or absence (n = 79, 75%) of silent CAD defined by concordant abnormal exercise electrocardiographic testing and thallium-201 myocardial scintigraphy. The male sex, the severity of the symptomatic carotid lesion (>90%), and the coexistence of contralateral carotid disease identified patients with higher probability of coexisting CAD. The 106 patients underwent 121 operations (bilateral in 15). In the perioperative period, no deaths or cardiac events occurred, 1 patient suffered a recurrent stroke and 3 had a transient ischemic attack. During a mean follow-up period of 5.4 years, 9 patients died (1.7%/year): fatal myocardial infarction occurred in 5 (all in the silent CAD group), cancer in 3 and vertebrobasilar stroke in 1. Nonfatal events occurred in 9 patients: myocardial infarction in 1 (without silent CAD), unstable angina in 3 (with silent CAD), and cerebral ischemic attacks in 5. After 7 years, the Kaplan-Meier estimated survival free from coronary events was 51% in patients with silent CAD, and 98% in patients without CAD ($p < 0.01$).

In conclusion, among patients with symptomatic high-grade carotid stenosis undergoing carotid endarterectomy, even in absence of history or symptoms of CAD, a silent CAD is detectable in one fourth of the patients. Silent CAD did not affect the perioperative outcome, but strongly influenced the long-term prognosis. These results suggest the need for routine screening of silent CAD in patients with severe carotid stenosis to identify those at high long-term risk of cardiac events, for whom a more aggressive management should be warranted.

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Patients with transient ischemic attacks or stroke are at high risk for coronary artery events.[1–4] The cardiac mortality of 5%/year, observed in the follow-up of patients with cerebral ischemia, exceeds even the cardiac mortality rate of patients with angina pectoris, so that a cerebral ischemic attack should be considered a warning signal of future cardiac events.[5] In patients with symptomatic high-grade carotid stenosis undergoing carotid endarterectomy, myocardial infarction accounts for one-half of perioperative deaths[6,7]; during the long-term follow-up, the risk of fatal myocardial infarction is 2 to 5 times greater than the risk of fatal stroke.[6–10] Whereas the risk of cardiac events is well known in patients with a history of myocardial infarction or angina who are undergoing carotid endarterectomy, no data are available concerning the cardiac risk in patients with clinically silent coronary artery disease (CAD). The aim of the present study is to assess the prevalence and prognostic role of silent CAD in patients with no history, symptoms or electrocardiographic (ECG) signs of cardiac disease who are undergoing carotid endarterectomy for symptomatic high-grade carotid stenosis.

METHODS

Patients: One hundred six consecutive patients admitted to the Department of Neurosurgery of our hospital for carotid endarterectomy fulfilled the following inclusion criteria: (1) transient ischemic attack or minor stroke of the carotid territory; (2) high-grade carotid stenosis (70 to 99%), ipsilateral to cerebral symptoms; (3) no history, symptoms or ECG signs of CAD; and (4) ability to perform adequate exercise ECG testing.

Basal investigation: Patients underwent a standardized neurologic investigation consisting of history, neurologic examination, computed tomography scan of the brain and 4-vessel cerebral angiography. The cardiologic investigation consisted of history, physical examination, 12-lead electrocardiogram, chest x-ray, 2-dimensional echocardiography, exercise ECG testing and, in patients with abnormal exercise ECG testing, thallium-201 myocardial scintigraphy. Silent CAD was defined by concordant, abnormal exercise ECG testing and thallium-201 myocardial scintigraphy.

Exercise electrocardiographic testing: Exercise ECG testing was performed by treadmill, using a Marquette Case II recorder, according to a modified Bruce protocol (exercise stages of 2 minutes starting from level 0). Patients with bundle branch block and left ventricu-

lar hypertrophy were excluded from the study. A 12-lead electrocardiogram and blood pressure were recorded before, at the end of each stage, at peak exercise and at 2-minute intervals in the recovery phase. During exercise the 12 ECG leads were continuously monitored. Exercise ECG testing was maximal or limited by exhaustion, symptoms, systolic blood pressure ≥240 mm Hg, or ST-segment depression ≥3 mm. Exercise ECG testing was considered abnormal if ST depression ≥1 mm or ST elevation ≥1.5 mm were present.

Thallium-201 myocardial scintigraphy: Patients with abnormal results on exercise ECG testing underwent bicycle exercise thallium-201 myocardial imaging within 2 weeks. At the appearance of at least 1.0 mm ST-segment depression, 74 MBq of thallium-201 were injected intravenously, and the patient was requested to continue the exercise for another 60 to 90 seconds. Each patient underwent imaging in the supine position with a PHO gamma V scintillation camera immediately and after isotope administration (exercise), and 4 hours later (delayed test) for the redistribution scan. Each image was subdivided into 3 or 4 segments corresponding to the territories of distribution of left anterior descending, circumflex and right coronary arteries for a total of 8 segments. Images were stored in a computer for processing, semiquantitative analysis, and elaboration of circumferential profiles.

Treatment and follow-up: Preoperatively, during and after surgery, patients with silent CAD were treated with β blockers and nitrates. Nifedipine was administered if β blockers were contraindicated. Aspirin or ticlopidine were given to all patients after surgery. During the follow-up, a neurologic and cardiologic evaluation was done every 6 months. Patients with silent CAD performed exercise ECG testing every year. Medical therapy, initiated before surgery in patients with CAD (aspirin, β blockers, and so forth), was continued during the follow-up.

Statistical analysis: Continuous data are given as mean ± standard deviation. Student's *t* test was used for differences between the mean of different observations, and the chi-square test to determine the difference between proportions. The occurrence of new cardiac events was compared between groups of patients by the construction of Kaplan-Meyer survival curves. A p value <0.05 was required for statistical significance.

RESULTS

Study population: Patients were aged 58.7 ± 8.4 years (range 42 to 73) and 76 (72%) were men. According to the inclusion criteria no patient had a history or symptoms of CAD. Echocardiograms never showed evidence of wall motion abnormalities and the ejection fraction was ≥45% in all patients.

Exercise ECG testing was abnormal in 39 patients (37%) without angina. All these patients underwent thallium-201 myocardial scintigraphy, which confirmed a silent CAD in 27 (25% of the study population) (perfusional defects of 2.2 ± 0.9 segments, reversible in all patients). Among the 27 patients with silent CAD and the remaining 79, there were no significant differences for age, atherosclerotic risk factors, transient ischemic attack or stroke prevalence, and coexistence of intermittent claudication. In patients with CAD, the male prevalence was significantly higher (p <0.05) (Table I). A carotid stenosis of 70 to 90% was observed in 13 patients (48%) with CAD and in 59 (75%) without CAD. Conversely, a more severe carotid stenosis of 90 to 99% was observed in 14 patients (52%) with CAD and in 20 (25%) without CAD (p <0.01). A contralateral carotid occlusion or stenosis ≥70% was observed in 17 patients (63%) with CAD and in 30 (38%) without CAD (p <0.05). Finally, the presence of ischemic areas at computed tomography scan of the brain was similar in the 2 groups (Table II).

TABLE I Distribution of Conventional Risk Factors and Type of Cerebral Ischemia by Presence of Silent Coronary Artery Disease

	CAD		
	Absent (n = 79) n (%)	Present (n = 27) n (%)	p Value
Mean age (yr)	65 ± 8	64 ± 7	NS
Men/women	51 (65)/28 (35)	24 (89)/3 (11)	<0.05
Current smoking	54 (68)	20 (74)	NS
Systemic hypertension	45 (57)	16 (59)	NS
Diabetes mellitus	17 (21)	5 (18)	NS
Hypercholesterolemia (≥200 mg/dl)	34 (43)	11 (41)	NS
Claudication	22 (28)	6 (22)	NS
Transient ischemic attack	61 (77)	20 (74)	NS
Stroke	18 (23)	7 (26)	NS

CAD = coronary artery disease; NS = not significant.

TABLE II Severity of Symptomatic Carotid Lesions, and Prevalence of Contralateral Carotid Disease and Ischemia at Computed Tomography Scan of the Brain by Presence of Silent Coronary Artery Disease

	CAD		
	Absent (n = 79) n (%)	Present (n = 27) n (%)	p Value
Ipsilateral carotid lesion			
70–90%	59 (75)	13 (48)	<0.01
90–99%	20 (25)	14 (52)	
Contralateral carotid lesions (≥70%)			
Presence	30 (38)	17 (63)	<0.005
Absence	49 (62)	10 (37)	
Computed tomography brain scan			
Ischemia	34 (43)	11 (41)	NS
Normal	45 (57)	26 (59)	

CAD = coronary artery disease; NS = not significant.

Perioperative outcome: The 106 patients underwent 121 operations (9 had bilateral carotid endarterectomies and 6 a contralateral extraintracranial arterial bypass). No deaths occurred during the perioperative period (within 30 days after surgery). One patient had carotid stroke, ipsilateral to the surgical lesion, and 3 patients had a transient ischemic attack (Table III).

Long-term prognosis: During a mean follow-up period of 5.4 years, 9 patients died (1.7%/year): a fatal myocardial infarction occurred in 5 (all with silent

TABLE III Morbidity and Mortality in 106 Patients Undergoing Carotid Endarterectomy

	CAD	
	Absent (n = 79) n (%)	Present (n = 27) n (%)
Early (< 30 days)		
Total deaths (n = 0)		
Nonfatal events (n = 4)		
Myocardial infarction	0	0
Transient ischemic attack	2	1
Stroke	0	1
Late (> 30 days)		
Total deaths (n = 9)		
Myocardial infarction	0	5
Cancer	3	0
Stroke	1	0
Nonfatal events (n = 9)		
Myocardial infarction	1	0
Unstable angina	0	3
Transient ischemic attack	3	0
Stroke	2	0

CAD = coronary artery disease.

TABLE IV Exercise ECG Testing and Thallium-201 Myocardial Scintigraphy Findings in Patients with Silent CAD as to the Presence of Coronary Events During a Mean Follow-Up of 5.4 Years

	Silent CAD (n = 27)		
	Coronary Events (n = 8)	No Coronary Events (n = 19)	p Value
Exercise ECG testing			
Total duration (min)	6.2 ± 1.1	6.4 ± 1.7	NS
Onset of 1 mm ST depression (min)	3.2 ± 2.1	4.9 ± 2.4	NS
Rate-pressure product at onset 1 mm ST depression ($\times 10^3$)	15.4 ± 4.6	21.3 ± 4.9	<0.05
Max. ST depression (mm)	2.5 ± 0.5	2.1 ± 0.7	NS
Rate-pressure product at peak exercise ($\times 10^3$)	21.0 ± 4.9	27.1 ± 4.8	<0.05
Persistence of ST depression in the recovery phase (min)	7.8 ± 1.5	5.2 ± 4.2	NS
Thallium-201 myocardial scintigraphy			
Extent of perfusion defects (segments)	2.6 ± 1.1	2.0 ± 0.7	NS

ECG = electrocardiographic; other abbreviations as in Table I.

CAD at preoperative evaluation), cancer in 3, and vertebrobasilar stroke in 1. Nonfatal myocardial infarction occurred in 1 patient with normal preoperative cardiac evaluation, and 3 patients with silent CAD became symptomatic for unstable angina. During the follow-up, recurrences of cerebral ischemia occurred in 5 patients (Table III). Among patients with silent CAD the rate-pressure product at 1 mm ST-segment depression and at peak exercise were the only parameters of exercise ECG testing predictive of coronary events during the follow-up, whereas the extent of myocardial ischemia at thallium-201 myocardial scintigraphy was not significantly different between the 2 groups (Table IV). Coronary angiography was performed in a patient with very low threshold of silent ischemia and, during the follow-up, in the 2 patients who developed unstable angina. These three patients later underwent coronary revascularization.

After 7-year follow-up, Kaplan-Meyer estimated survival free from fatal and nonfatal coronary events was 51% in patients with silent CAD and 98% in patients without CAD at preoperative evaluation ($p < 0.01$) (Figure 1).

DISCUSSION

Cardiac events in patients undergoing carotid endarterectomy: Patients with symptomatic, severe carotid stenosis, undergoing carotid endarterectomy have a high risk of coronary events both during the perioperative pe-

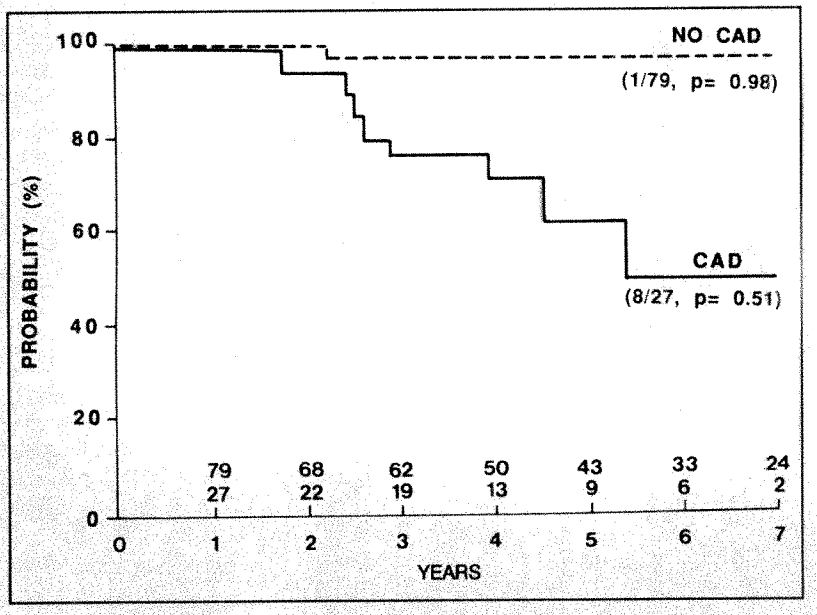


FIGURE 1. Probability of survival free from fatal and nonfatal coronary events in patients undergoing carotid endarterectomy. After 7-year follow-up, the probability was 51% in patients with silent coronary artery disease (CAD) and 98% in those without CAD.

riod or in the follow-up. Hertzer et al,[11] in a series of 390 patients undergoing carotid endarterectomy, observed a perioperative myocardial infarction in 4% of those with a history of CAD, and in 0.5% of the control subjects. During a follow-up period of 1 to 11 years, a fatal myocardial infarction occurred in 25% of patients with known CAD and in 13% of the others. Ennix et al[12] reported perioperative mortality rates (due mainly to myocardial infarction) of 18% in cerebrovascular patients with angina pectoris and 1.5% in the control patients. Yeager et al[13] observed perioperative myocardial infarction in 6% of patients with active CAD, in 3% of those with a history of CAD, and in 1.5% of control patients. During a 21-month follow-up, the death rate was 15.2, 12.5 and 10.2%, respectively. Early and late survival, however, were similar in the 3 groups ($p < 0.05$). Recently, among patients who underwent carotid endarterectomy, Mackey et al[14] found that patients with overt CAD had reduced 30-day ($p = 0.03$) and late survival ($p < 0.0001$). In the latter study, among patients without overt CAD, the presence of coronary risk factors identified those with worse prognosis.

Need for a routine investigation of coronary artery disease: The diagnosis of CAD in patients undergoing carotid endarterectomy is usually based on history of myocardial infarction, angina pectoris or "ischemic" ST segment on the electrocardiogram at rest. Since a standardized cardiac investigation is not routinely performed, even in patients without history or clinical signs of cardiac disease, the prevalence of CAD in this population may be underestimated. Whisnant et al[15] suggested that the poor relationship between the clinical evidence of CAD and the survival rate after a stroke could be explained by the unknown prevalence of silent CAD in patients without overt cardiac disease. The high prevalence of silent CAD in patients with cerebral ischemia was first assessed, a few years ago, in a large angiographic study of 200 patients without history or symptoms of CAD, undergoing carotid endarterectomy. Coronary lesions were identified in 86% of patients, severe (≥70%) in 40%.[16]

Nevertheless, a screening based on coronary angiography in patients undergoing carotid endarterectomy has an unfavorable cost-effectiveness ratio. A noninvasive evaluation consisting of exercise ECG testing and thallium-201 myocardial scintigraphy should be considered a reliable alternative, their sensitivity and specificity being high in a population with a high prevalence of CAD.[17-20] In previous noninvasive studies the prevalence rate of CAD in cerebrovascular patients was 10 times greater than in a control group of healthy subjects,[21,22] although the real prevalence of silent CAD is probably underestimated because of the study protocol used. Moreover, in patients unable to exercise, a silent CAD was identified by dipyridamole myocardial imaging in >50% of the patients.[23]

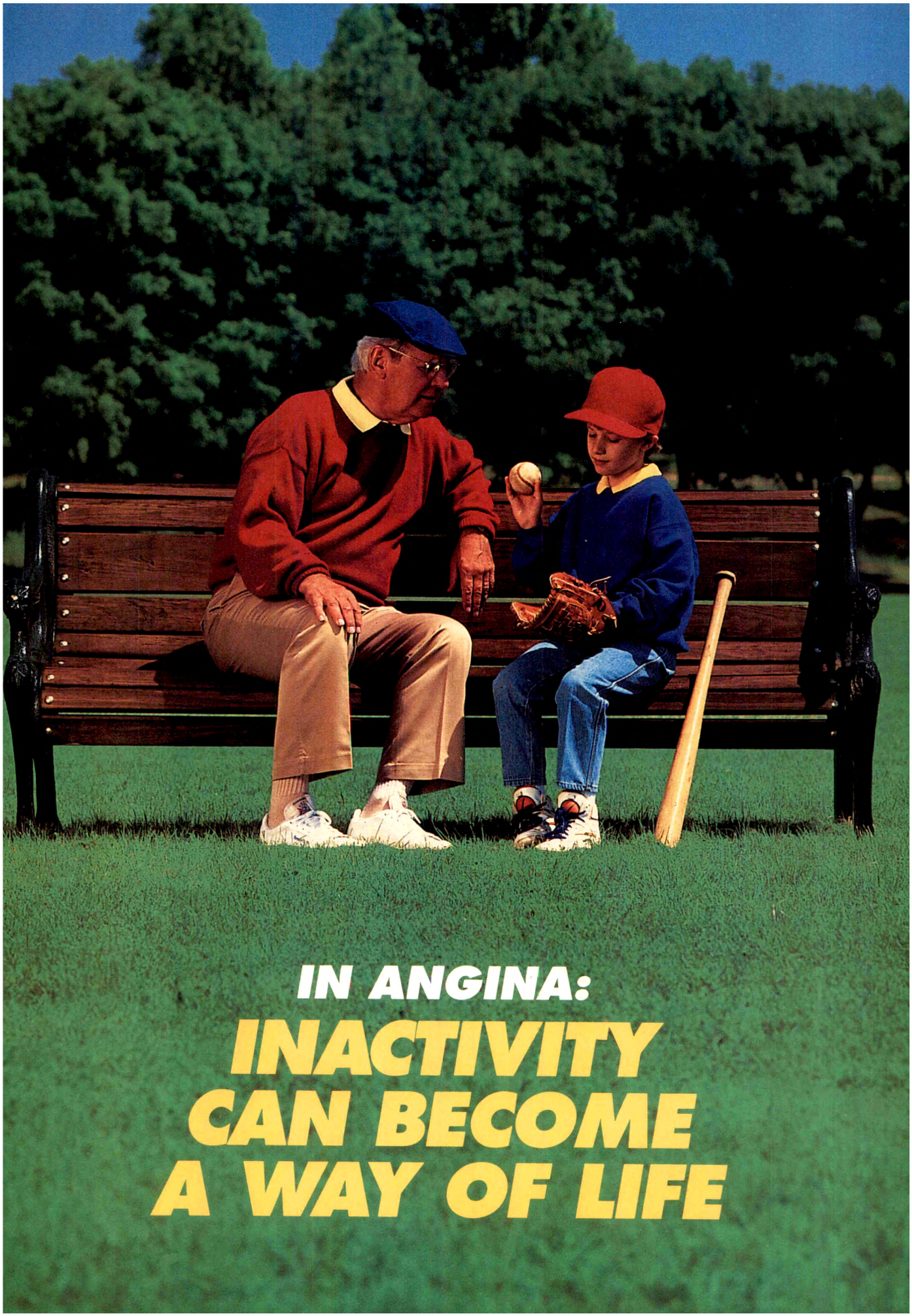
Clinical implications: The present study first assessed the prevalence of silent CAD in patients with neither history nor symptoms of CAD undergoing carotid endarterectomy. One fourth of these patients showed abnormal concordant exercise ECG testing and myocardial scintigraphy. Furthermore, in patients with silent CAD, the severity of the carotid lesions and the coexistence of contralateral carotid disease were significantly greater. Silent CAD did not affect the perioperative outcome in patients given adequate anti-ischemic therapy, but strongly influenced the long-term prognosis. During a 5.4-year follow-up, coronary events occurred in 29% of patients with silent CAD, but in only 1.2% of those without CAD; the probability of survival free from coronary events is significantly worse in patients with silent CAD. Most deaths were of cardiac origin and all the patients who died from myocardial infarction had CAD on preoperative evaluation.

Conclusions: Whereas 2 large randomized clinical trials have recently demonstrated that carotid endarterectomy can significantly improve the neurologic prognosis of patients with symptomatic high-grade carotid stenosis,[10,24] the unfavorable cardiologic long-term prognosis suggests the need for careful cardiac evaluation of these patients. According to our experience, and recent studies dealing with patients undergoing vascular surgery,[25] a noninvasive screening for CAD should be performed in all patients undergoing carotid endarterectomy, even in those without history or symptoms of CAD, in order to identify patients who need more aggressive monitoring and management during the follow-up.

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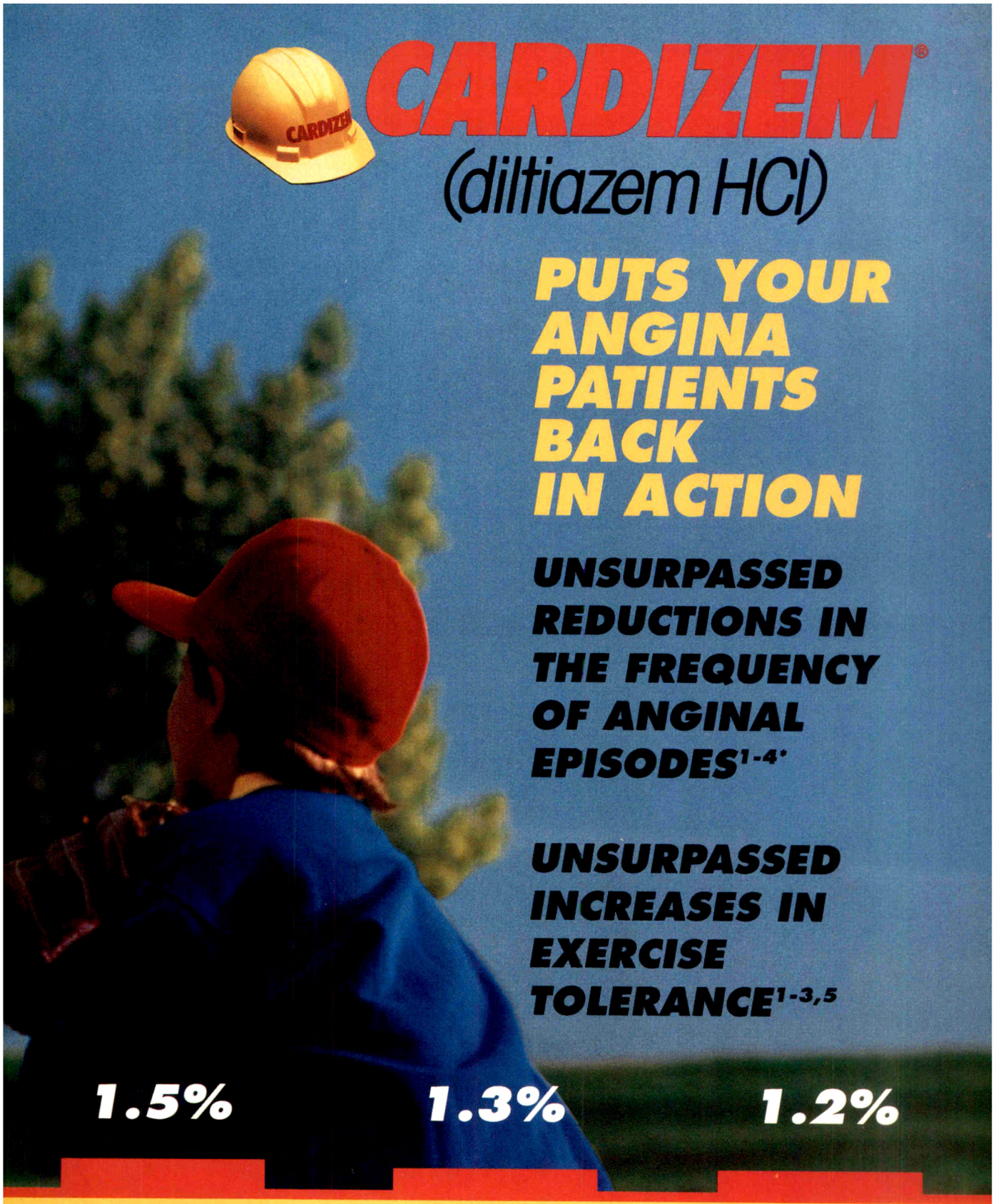


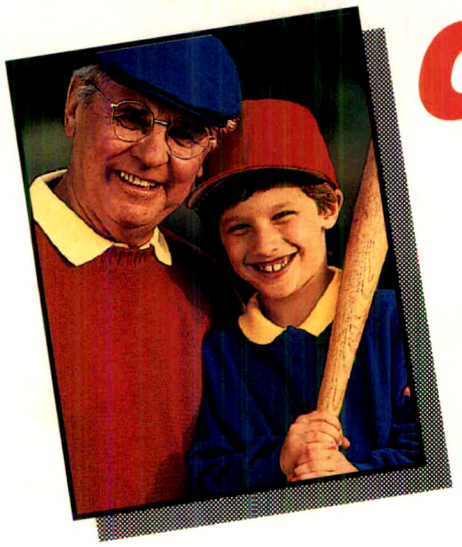
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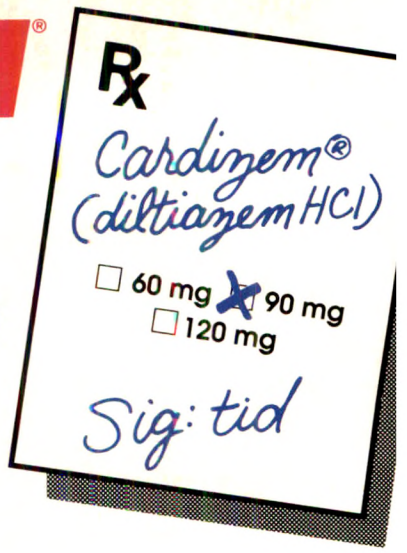
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BRIEF SUMMARY

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WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the curve (53%) after a 1-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled angina trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies of angina patients. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences from these studies, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular: Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, bundle branch block, congestive heart failure, ECG abnormality, flushing, hypotension, palpitations, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tremor.

Gastrointestinal: Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK elevation, dry mouth, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between these events and CARDIZEM therapy cannot yet be established. Exfoliative dermatitis (proven by rechallenge) has also been reported.

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Coronary Vasodilatory Action of Elgodipine in Coronary Artery Disease

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The effects of intravenous elgodipine, a new second-generation dihydropyridine calcium antagonist, on hemodynamics and coronary artery diameter were investigated in 15 patients undergoing cardiac catheterization for suspected coronary artery disease. Despite a significant decrease in systemic blood pressure, elgodipine infused at a rate of 1.5 μg/kg/min over a period of 10 minutes did not affect heart rate and left ventricular end-diastolic pressure. The contractile responses during isovolumic contraction showed a slight but significant increase in maximum velocity (56 ± 10 to 60 ± 10 seconds^{-1}; p <0.005), whereas the time constant of early relaxation was shortened from 49 ± 11 to 44 ± 9 ms (p <0.05). Coronary sinus and great cardiac vein flow increased significantly by 15 and 26%, respectively. As mean aortic pressure decreased, a significant decrease in coronary sinus (−27%) and great cardiac vein (−28%) resistance was observed, while the calculated myocardial oxygen consumption remained unchanged. In all, 69 coronary segments (including 13 stenotic segments) were analyzed quantitatively using computer-assisted quantitative coronary angiography. A significant increase in mean coronary artery diameter (2.27 ± 0.53 to 2.48 ± 0.53 mm; p <0.000001), as well as in obstruction diameter, (1.08 ± 0.29 to 1.36 ± 0.32 mm; p <0.02), was observed. The results demonstrate that elgodipine, in the route and dose described, induces significant vasodilatation of both coronary resistance and epicardial conductance vessels, without adverse effects on heart rate, myocardial oxygen demand and contractile indexes.

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Elgodipine (isopropyl (2-(N-methyl-N-(4-fluorobenzyl)-amine)-ethyl, 2,6-dimethyl-4-(2′,3′-methylenedioxypheynl)-1,4-dihydropyridine-3,5-dicarboxylate, monohydrochloride) is a newly synthesized drug with calcium entry blocking properties belonging to the second generation of the phenyldihydropyridine group.[1,2] In vitro studies have shown that the drug appears to be 100-fold more potent in inducing vasodilatation than in causing negative inotropic effects[1] and that when comparing different vascular beds, the most pronounced vasodilatory effect was in the coronary vasculature.[3] This relative selectivity of elgodipine for the coronary vascular bed may be of particular significance in patients with coronary artery disease where an imbalance in myocardial oxygen supply and demand is caused by decrease in the coronary artery luminal diameter. Animal studies[3,4] have demonstrated that elgodipine is a potent vasodilator, decreasing blood pressure and total peripheral resistance, and increasing cardiac output and coronary blood flow dose-dependently, with little effect on heart rate. The potency of elgodipine in reducing systemic vascular resistance is slightly less than that of nifedipine, nisoldipine and nimodipine, but considerably greater (10- to 50-fold) than that of bepridil, nicorandil and pimobendan.[3] These effects of elgodipine on systemic and coronary hemodynamics have yet to be evaluated in patients with coronary artery disease. The present study investigates the effects of intravenous elgodipine on coronary and left ventricular hemodynamics, and assesses quantitatively the vasodilatory action of elgodipine on both stenotic and nonstenotic coronary arteries, using computer-assisted quantitative coronary angiography.

METHODS

Patients: The study comprised 15 patients (12 men and 3 women, mean age 57 years, range 40 to 69) who underwent cardiac catheterization for the investigation of suspected coronary artery disease. All patients were in sinus rhythm with no signs of cardiac failure and gave informed consent to participate in the study. Patients with unstable angina and acute myocardial infarction were excluded from the study. Clinical and angiographic data are listed in Table I.

Protocol: All medication was discontinued ≥48 hours before the study. Cardiac catheterization was performed through the femoral artery and vein. Patients fasted and were not given premedication. No drug (other than 50 mg of intravenous heparin) was administered during the study. After a thermodilution flow catheter was inserted in the coronary sinus and great cardiac vein, angiography of the right and left coronary artery

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TABLE I Clinical Characteristics

Pt.	Age (yr) & Sex	NYHA	PMI	EF (%)	Coronary Artery Narrowed >50% in Diameter		
					LAD	LC	Right
1	43F	II	0	70	0	0	+
2	66M	III	Anterior	49	+	+	+
3	68M	II	0	50	+	+	+
4	64M	I	Inferior	41	+	0	+
5	55M	II	0	62	0	+	0
6	63M	II	0	77	0	+	+
7	40M	II	Anterior	67	+	0	0
8	44M	II	Anterior	—	+	0	0
9	60M	II	Inferior	—	+	+	+
10	59M	II	Anterior	62	+	0	0
11	51F	II	0	65	0	0	0
12	64M	II	Inferior	66	+	+	+
13	69F	II	0	64	+	0	0
14	44M	II	Inferior	55	+	+	+
15	62M	II	Anterolateral	71	0	+	0

EF = global ejection fraction; LAD = left anterior descending; LC = left circumflex; NYHA = New York Heart Association classifications; PMI = previous myocardial infarction.

was performed in standard views including cranial and caudal angulations. The geometry of the x-ray gantry, and the kilovolts and milliamperes of the x-ray generator were obtained and recorded on-line for each angiogram. A dual-tip micromanometer catheter was then positioned in the left ventricle. Ten minutes after catheter instrumentation, baseline left ventricular and aortic pressures, pressure-derived indexes of isovolumic contraction and relaxation, and thermodilution coronary sinus and great cardiac vein flows were measured on-line at spontaneous heart rate. Oxygen saturations were obtained simultaneously from the aorta, coronary sinus and great cardiac vein. Elgodipine was then administered intravenously at a rate of 1.5 μg/kg/min over a period of 10 minutes, and all measurements were repeated at 5, 10, 20 and 30 minutes. Angiography of the left coronary artery was repeated at 10 and 30 minutes in all projections, corresponding to those used during baseline angiography. All angiograms were obtained using the Judkins technique and recorded on Kodak 35 mm cinefilm at a rate of 25 frames/second. Nonionic contrast medium was injected manually.

Hemodynamic determinations: Left ventricular parameters were measured at spontaneous heart rate using the dual-tip micromanometer catheter, where ≥12 heart beats were processed and averaged on-line by means of the representative beat method in a dedicated computer system.[5,6] The following left ventricular pressure-derived indexes of isovolumic contraction and relaxation were computed: peak left ventricular pressure, end-diastolic pressure, peak first derivative of left ventricular pressure (dP/dt), peak left ventricular dP/dt/p from total pressure providing p >20 mm Hg (peak V_{CE}), dP/dt/p linearly extrapolated to 0 mm Hg (Vmax), and the time constants for early relaxation (Tau), a semilogarithmic biexponential fit of the left ventricular pressure decay characterized by 2 exponential time constants: Tau1 for the first 40 ms, and Tau2, the fit after the first 40 ms.[7] Mean aortic pressure was determined by digital integration.

Coronary venous blood flow measurements and calculations: Coronary sinus and great cardiac vein blood flows were measured on-line using a constant infusion thermodilution technique. Arterial, coronary sinus and great cardiac vein oxygen saturations were measured

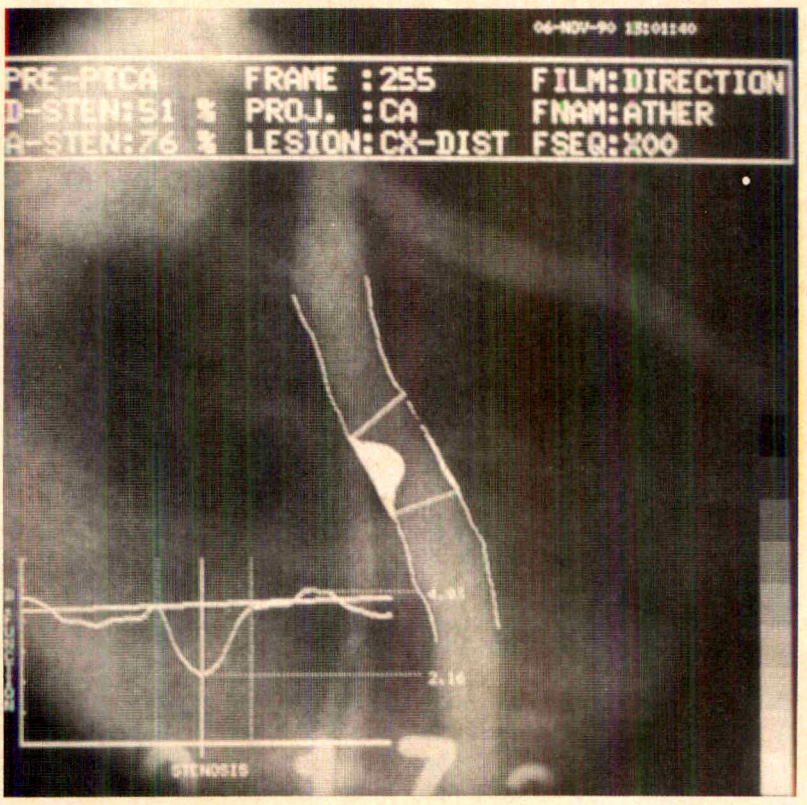


FIGURE 1. One cineframe of distal left circumflex (CX-DIST) coronary artery in caudal (CA) projection is shown with detected contours and diameter functions superimposed on original video image. On basis of proximal and distal segments, reference contours over obstructed region are reconstructed by interpolated diameter technique. Minimal obstruction and reference diameters are expressed in millimeters. In this case, reference diameter is 4.03 mm, and obstruction diameter is 2.16 mm, corresponding to diameter stenosis (D-STEN) of 51%, and area stenosis (A-STEN) of 76%. PTCA = percutaneous transluminal coronary angioplasty.

TABLE II Effects on Systemic and Left Ventricular Hemodynamics

	Baseline	5 Minutes	10 Minutes	20 Minutes	30 Minutes
Heart rate (beats/min)	70 ± 10	73 ± 11	75 ± 14	73 ± 18	70 ± 12
Systolic aortic pressure (mm Hg)	145 ± 24	130 ± 24*	123 ± 22*	140 ± 32	138 ± 23
Diastolic aortic pressure (mm Hg)	70 ± 9	65 ± 9‡	61 ± 8*	69 ± 15	70 ± 11
Mean aortic pressure (mm Hg)	98 ± 15	90 ± 15*	86 ± 14*	97 ± 23	97 ± 14
Left ventricular systolic pressure (mm Hg)	139 ± 22	126 ± 22*	117 ± 20*	133 ± 29	133 ± 21†
End-diastolic pressure (mm Hg)	13 ± 3	12 ± 4	13 ± 4	13 ± 4	12 ± 5
Peak V_{CE} (sec^{-1})	39 ± 9	42 ± 12	42 ± 13	39 ± 10	39 ± 9
Vmax (sec^{-1})	56 ± 10	57 ± 9	60 ± 10‡	57 ± 10	54 ± 9
Positive dP/dt (mm Hg sec^{-1})	1,485 ± 308	1,467 ± 319	1,496 ± 396	1,565 ± 489	1,453 ± 308
Negative dP/dt (mm Hg sec^{-1})	1,743 ± 354	1,673 ± 350†	1,637 ± 359‡	1,727 ± 383	1,712 ± 358
Tau1 (ms)	49 ± 11	46 ± 8†	44 ± 9†	47 ± 11	48 ± 11

*p <0.00005; †p <0.05; ‡p <0.005 vs baseline.
Values are expressed as mean ± SD.
dP/dt = rate of change in left ventricular pressure; Peak V_{CE} = peak measured velocity of contractile element; Tau1 = time constant of early relaxation; Vmax = V_{CE} linearly extrapolated to 0 mm Hg.

spectrophotometrically, and oxygen content was calculated. Global (coronary sinus) and regional (great cardiac vein) myocardial oxygen consumptions were calculated as the product of coronary venous blood flow and arteriocoronary venous oxygen content difference. Global and regional coronary vascular resistances were derived from the ratio of mean aortic pressure to coronary venous flow.

Quantitative coronary angiography: Quantitative analysis of selected coronary segments was performed with the computer-assisted cardiovascular angiography analysis system that was described in detail previously.[8,9] Briefly, to analyze a coronary arterial segment in a selected frame of 35 mm cinefilm, an optically magnified portion of the image encompassing that segment is converted into video format by means of a cinevideo converter. The contours of the vessels are detected automatically on the basis of the weighted sum of first and second derivative functions applied to the digitized brightness information. Calibration of the diameter data of the vessels in absolute values (mm) is achieved using the angiographic catheter filmed empty of contrast. To this end, the contours of a user-defined portion of the optimally magnified catheter are detected automatically and corrected for pincushion distortion caused by the image intensifier. From the contours, vessel diameter functions (in absolute mm) are determined by computing the shortest distances between the left and right contour positions. A representative analysis with the detected contours and diameter functions superimposed on the original video image is shown in Figure 1. For nonobstructed coronary segments, the mean diameter of the analyzed segment was computed. For obstructed segments, the minimal obstruction diameter was assessed. Average values for baseline, and 10- and 20-minute angiograms obtained from ≥2 orthogonal angiographic views were compared.

Theoretical pressure gradient across stenotic lesions: For obstructed coronary segments, the theoretical pressure gradients across the stenotic lesion at theoretical coronary flow rates of 1, 2 and 3 ml/s were calculated using the data obtained at quantitative angiographic analysis according to an accepted formula[10,11]: $P_{GRAD} = Q \cdot (R_P + Q \cdot R_T)$, where P_{GRAD} is the theoretical pressure reduction (mm Hg) across the stenosis, Q is the mean coronary blood flow (ml/s), R_P is the Poiseuille resistance, and R_T is the turbulent resistance. These resistances have been defined as follows:

$$R_P = C_1 \times \frac{(\text{length obstruction}) \times \pi}{(\text{obstruction area})^2}$$

where $C_1 = 8 \times$ (blood viscosity), with blood viscosity = 0.03 (g/cm · s), and

$$R_T = C_2 \times \left(\frac{1}{\text{obstruction area}} - \frac{1}{\text{normal distal area}}\right)^2$$

where C_2 = blood density/0.266, with blood density = 1.0 (g/cm^3). This assessment of pressure gradients was used and described in our previous studies.[12-14]

Statistical analysis: Results are expressed as mean ± SD. The data was subjected to analysis of variance for repeated measurements, and when significant differences were apparent, further comparisons were made with Student's paired *t* test. A p value <0.05 was considered significant.

RESULTS

Systemic hemodynamics: The systemic responses after intravenous administration of elgodipine at a rate of 1.5 μg/kg/min over 10 minutes are listed in Table II. At spontaneous heart rate, elgodipine produced a significant decrease in aortic pressure, while heart rate did not change significantly. During elgodipine infusion, left ventricular systolic pressure decreased significantly by 16% (p <0.00005), while end-diastolic pressure remained unchanged (Table II). Although the increase in peak V_{CE} did not reach statistical significance, Vmax was significantly increased (56 ± 10 to 60 ± 10 $seconds^{-1}$; p <0.005), whereas Tau1 was shortened (49 ± 11 to 44 ± 9 ms; p <0.05). At 20 minutes, all parameters were no longer significantly different from baseline.

Coronary hemodynamics: After elgodipine infusion, coronary sinus and great cardiac vein blood flows increased significantly (75 ± 26 to 86 ± 30 ml/min [p

TABLE III Effects on Coronary Hemodynamics

	Baseline	5 Minutes	10 Minutes	20 Minutes	30 Minutes
Coronary sinus flow (ml/min)	75 ± 26	81 ± 30*	86 ± 30†	83 ± 27‡	81 ± 28‡
Great cardiac vein flow (ml/min)	34 ± 10	38 ± 13‡	43 ± 13*	39 ± 12	36 ± 10
Oxygen difference (aortocoronary sinus) (ml%)	13.9 ± 1.7	13.1 ± 1.5*	11.9 ± 1.5§	12.4 ± 1.5*	13.2 ± 1.3*
Oxygen difference (aorta great cardiac vein) (ml%)	13.9 ± 1.7	13.2 ± 1.5*	12.0 ± 1.5†	12.5 ± 1.1*	13.0 ± 1.4*
Global myocardial oxygen consumption (ml/min)	10.2 ± 3.0	10.4 ± 3.4	10.1 ± 3.3	10.3 ± 3.4	10.5 ± 3.3
Regional myocardial oxygen consumption (ml/min)	4.8 ± 1.2	5.1 ± 1.5	5.2 ± 1.5	5.1 ± 1.6	4.7 ± 1.1
Coronary sinus resistance (mm Hg/ml/min)	1.5 ± 0.5	1.3 ± 0.5†	1.1 ± 0.3§	1.3 ± 0.4‡	1.3 ± 0.5
Great cardiac vein resistance (mm Hg/ml/min)	3.2 ± 1.4	2.7 ± 1.4*	2.3 ± 1.2†	2.7 ± 1.1‡	3.0 ± 1.3

*p <0.005; †p <0.0005; ‡p <0.05; §p <0.00005 vs baseline.
Values are expressed as mean ± SD.

TABLE IV Effects on Absolute Coronary Artery Diameter (mm) in All Analyzed Segments

Coronary Artery Segment	Baseline	10 Minutes	p Value*	30 Minutes	p Value*
Left anterior descending					
Proximal (n = 15)	2.46 ± 0.50	2.69 ± 0.50	0.004	2.57 ± 0.47	0.06
Mid (n = 11)	2.53 ± 0.58	2.99 ± 0.52	0.05	2.67 ± 0.52	0.07
Distal (n = 14)	1.81 ± 0.27	2.03 ± 0.31	0.03	1.93 ± 0.28	0.03
Left circumflex artery					
Proximal (n = 15)	2.51 ± 0.51	2.55 ± 0.45	0.1	2.64 ± 0.48	0.004
Distal (n = 14)	2.06 ± 0.38	2.28 ± 0.43	0.0005	2.17 ± 0.42	0.04
Total (n = 69)	2.27 ± 0.53	2.48 ± 0.53	0.000001	2.39 ± 0.52	0.000001

*Versus baseline.
Values are expressed as mean ± SD.

TABLE V Effects on Stenotic Segments (n = 13)

	Baseline	10 Minutes	p Value*	30 Minutes	p Value*
Obstruction length (mm)	5.09 ± 2.12	5.32 ± 1.59	0.9	4.77 ± 1.25	0.1
Obstruction diameter (mm)	1.08 ± 0.29	1.36 ± 0.32	0.02	1.26 ± 0.33	0.03
Obstruction area (mm^2)	0.99 ± 0.67	1.56 ± 0.84	0.03	1.24 ± 0.77	0.09
Diameter stenosis (%)	58 ± 6	49 ± 8	0.008	52 ± 10	0.05
Area stenosis (%)	85 ± 9	78 ± 16	0.08	83 ± 13	0.5
Reference diameter (mm)	2.51 ± 0.52	2.72 ± 0.64	0.09	2.63 ± 0.44	0.05
Reference area (mm^2)	5.13 ± 1.98	6.11 ± 2.69	0.1	5.58 ± 1.70	0.08
Symmetry index	0.64 ± 0.18	0.59 ± 0.20	0.9	0.56 ± 0.22	0.2

*Versus baseline.
Values are expressed as mean ± SD.

<0.0005], and 34 ± 10 to 43 ± 13 ml/min [p <0.005], respectively; Table III). As mean aortic pressure decreased from 98 ± 15 to 86 ± 14 mm Hg (p < 0.00005), the calculated global and regional coronary vascular resistances decreased significantly (1.5 ± 0.5 to 1.1 ± 0.3 mm Hg/ml/min [p <0.00005], and 3.2 ± 1.4 to 2.3 ± 1.2 mm Hg/ml/min [p <0.0005], respectively). Although the differences in mean arteriocoronary sinus and arterio-great cardiac vein oxygen contents decreased from 13.9 ± 1.7 to 11.9 ± 1.5 ml% (p <0.00005) and from 13.9 ± 1.7 to 12.0 ± 1.5 ml% (p <0.0005), respectively, the global and regional myocardial oxygen consumptions remained unchanged.

Quantitative coronary angiograms: In all, 69 coronary segments (including 13 stenotic segments) of the left coronary artery were analyzed. The individual changes in absolute diameter (mm) of all coronary segments as measured during the 3 consecutive angiograms are listed in Table IV. Mean coronary diameter increased significantly from 2.27 ± 0.53 to 2.48 ± 0.53 mm (p <0.000001) at 10 minutes and to 2.39 ± 0.52 mm (p <0.000001) at 30 minutes after initiation of drug infusion.

Data for the 13 stenotic segments are listed in Table V. Mean obstruction diameter increased significantly from 1.08 ± 0.29 to 1.36 ± 0.32 mm (p <0.02) at 10 minutes and to 1.26 ± 0.33 mm (p <0.03) at 30 minutes after drug infusion was begun, whereas diameter stenosis decreased from 58 ± 6 to 49 ± 8% (p <0.008) and to 52 ± 10% (p <0.05), respectively. Consequently, assuming theoretical coronary flows of 1, 2 and 3 ml/s, the theoretical pressure gradients across the 13 stenotic lesions decreased significantly after elgodipine infusion (Figure 2).

DISCUSSION

The results of this study of patients with coronary artery disease confirm for the first time the beneficial effects of elgodipine, a newly synthesized dihydropyridine calcium antagonist, on systemic and coronary he-

modynamics previously suggested by animal experiments.[3,4]

Effects on heart rate: Several studies in anesthetized animals[3] showed that elgodipine is a potent systemic and coronary vasodilator, decreasing blood pressure and total peripheral resistance in a dose-dependent manner associated with an increase in coronary blood flow, whereas heart rate does not change or may even decrease in response to higher doses (60 μg/kg). Therefore, it is likely that (as observed with nimodipine)[15] elgodipine possesses some negative chronotropic activity[1] that counteracts reflex tachycardia. However, it should be appreciated that reflex tachycardia can be attenuated by anesthetic agents, reducing this phenomenon in anesthetized animals. To establish the cardiovascular profile of elgodipine, free of the potential influence of anesthetic agents, van Woerkens et al[4] investigated its effects in conscious instrumented pigs and observed a marked increase in heart rate, as well as in cardiac output and dP/dtmax. Although large doses of elgodipine were used, this may suggest that anesthesia in earlier studies blunted a reflex-mediated tachycardia. However, despite anesthesia, nisoldipine increases heart rate at a dose producing an equivalent reduction in systemic pressure.[16] Furthermore, when elgodipine is administered to conscious pigs after β-adrenoceptor blockade with propranolol, positive chronotropic and inotropic effects are substantially reduced, although an increase in heart rate is not completely eliminated.[4] This propranolol-resistant tachycardia is not unique to elgodipine, as it has also been observed for other dihydropyridines and vasodilators[17-22] and suggests a withdrawal of parasympathic tone.

In the present study, despite a marked decrease in aortic pressure, only a slight increase in heart rate was observed and this did not reach statistical significance

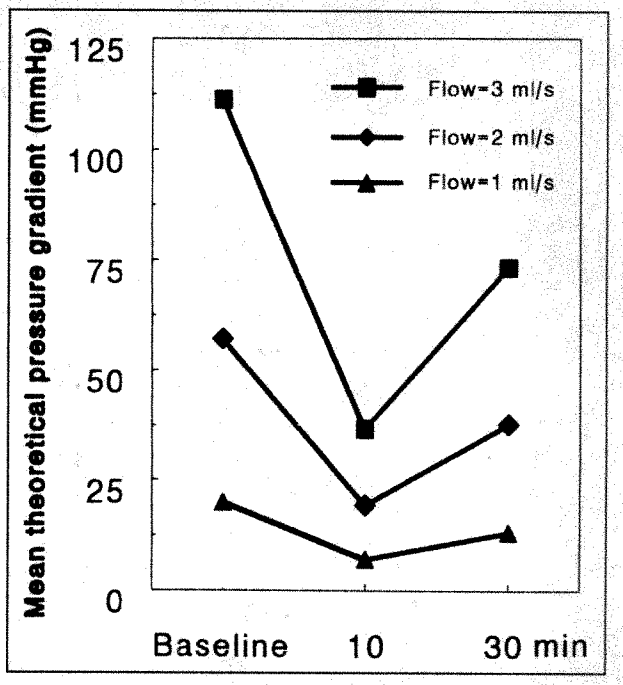


FIGURE 2. Changes in mean theoretical pressure gradient across stenotic lesion at theoretical coronary flows of 1, 2 and 3 ml/s.

(Table II). Although all cardiac medication (including β-blocking agents) was discontinued in all patients ≥48 hours before the study it may be speculated that β-adrenoceptor blockade could persist beyond this time and contributed to the lack of effect on heart rate. However, the resting heart rates of our study population suggest minimal β-blockade effect at the initiation of the study.

Effects on inotropic state: In vitro studies have shown that elgodipine appears to be 100-fold more po-

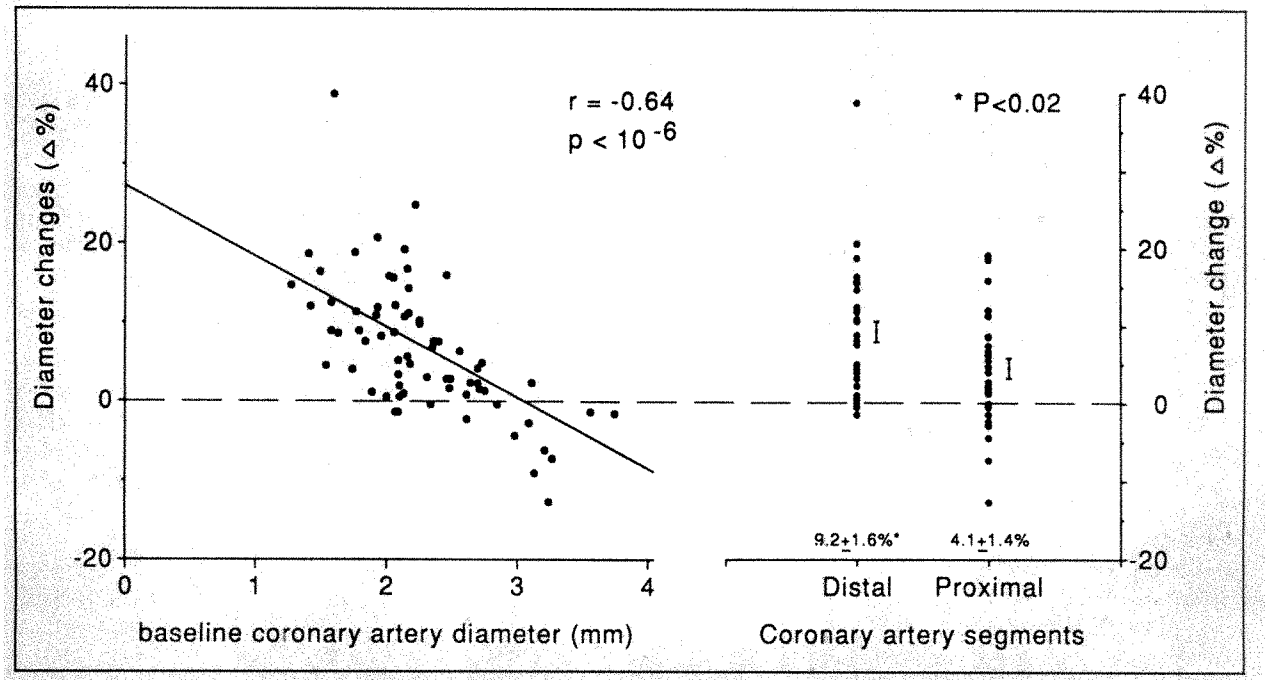


FIGURE 3. ***Left,*** **diameter changes during elgodipine infusion (at 10 minutes) compared with baseline mean coronary artery diameter.** ***Right,*** **diameter changes in proximal and distal parts of all analyzed coronary artery segments.**

tent as a vasodilator than as a negative inotrope.[1] In conscious animals, elgodipine produces dose-related increases in cardiac output and dP/dtmax, while left ventricular end-diastolic pressure (as with other dihydropyridines)[17] remains unchanged.[4] In conscious pigs with a 3- to 4-week-old myocardial infarction, the vasodilator responses to elgodipine are similar, although accompanied by considerably less of an increase in dP/dtmax compared with the effects in normal animals, but left ventricular end-diastolic pressure decreases significantly.[4] In the present study, elgodipine infusion led to a slight but significant increase in Vmax (Table II). Because heart rate and left ventricular end-diastolic pressure were unaffected, it may be suggested that, as used in the present study, the compound does not exert negative inotropic actions. However, our approach using isovolumic indexes could not entirely exclude the possibility of some negative inotropism. Furthermore, because elgodipine does not possess any β-adrenomimetic effects, this relatively positive inotropic response to the drug is probably not an intrinsic property of this new calcium antagonist, but rather related to its ability to induce peripheral vasodilation and reduce impedance to left ventricular ejection.

However, the absence of a negative inotropic effect of elgodipine is even more evident during intracoronary infusion[3]; 0.3 μg/kg/min substantially dilated the coronary vascular bed, but had only a minor effect on regional contractile function, whereas negative inotropic effects only became apparent at a rate of 0.9 μg/kg/min, which also affected systemic responses. Administered intravenously, a 30-fold greater dose would be needed to produce a negative inotropic effect, almost 20 times the dose administered in our study. Realistically, such a dose would not be clinically appropriate, because of the likelihood of severe hypotension.

Effects on isovolumic relaxation: Experimental work has emphasized the role of calcium influx–efflux in regulating the relaxation of the myocardial cell.[23] Left ventricular isovolumic relaxation is often abnormally prolonged in patients with coronary artery disease,[7,24,25] probably due to the presence of fibrotic scar tissue or still viable myocardium in which the biochemical process of activation (contraction and relaxation) has been altered by chronic ischemia.[25,26] Because it has been demonstrated that myocardial ischemia leads to asynergy of wall motion that can have a major role in altering the time course of the isovolumic pressure reduction,[26,27] it may be expected that an improvement of the asynergic zones would result in a more synchronous and rapid relaxation of the whole ventricle. In our study, Tau1 was significantly shortened after intravenous infusion of elgodipine (Table II). However, these results do not necessarily imply the intrinsic improvement of relaxation, but may be the indirect effects of a significant decrease in end-systolic pressure and volume.

Effects on coronary hemodynamics: Animal work has shown that intravenous elgodipine dose-dependently increases myocardial blood flow, with the greatest increase (up to 30%) occurring in the subepicardial layer.[3] In the presence of a simultaneous decrease in perfusion pressure, vasodilatation occurs in all layers of the myocardium to produce the necessary decrease in coronary vascular resistance, the decrease in the subepicardium (45%) being more pronounced than that (30%) in the subendocardium.[3] The present study confirms that elgodipine is a potent coronary vasodilator in humans. Coronary sinus and great cardiac vein flows increased significantly during elgodipine infusion by 15 and 26%, respectively. As mean aortic pressure dropped, substantial decreases in global (−27%) and regional (−28%) coronary vascular resistances were observed. The increase in coronary venous flow was associated with an increase in coronary venous oxygen saturation, resulting in a decrease in arteriocoronary venous oxygen content difference such that the calculated myocardial oxygen consumption did not decrease significantly (Table III). These results are consistent with our previous study of the effects of intravenous nisoldipine.[28]

Quantitative coronary angiography: To increase the accuracy of diameter measurements and to better reflect the true luminal cross-sectional area, multiple angiographic views ($\geq$2 orthogonal) were obtained in our study. If a coronary segment is nonaxisymmetric, vasodilation may accentuate the asymmetry of the lumen by preferentially relaxing the nonatherosclerotic part of the arterial wall. Consequently, the use of 1 angiographic view would be misleading. A relatively limited number of stenotic lesions was analyzed in this study owing to the following: (1) Selection needed high technical quality angiograms with clear views of the pre- and poststenotic segments; (2) orthogonal projections of the stenotic lesions were necessary; and (3) repeated angiography was limited to the left coronary artery.

Our results indicate that elgodipine induces significant vasodilatation not only in normal but also in stenotic coronary segments (Tables IV and V). The increase in the diameter of the nonstenotic segments was more pronounced in the distal and smaller sized segments than that in the larger proximal ones (Figure 3), as was previously observed with other vasodilatory agents.[29,30] Furthermore, the theoretical pressure gradients across the stenotic lesions (computed from the data obtained at quantitative coronary angiography) showed a considerable decrease after elgodipine administration (Figure 2).

Clinical implications: At the dose used in the present study, elgodipine did not produce any untoward effects and was consistently beneficial in terms of coronary hemodynamics. Therefore, elgodipine is of potential value for the treatment of ischemic heart disease and hypertension. Furthermore, the apparent absence of negative inotropic effects, and the reduction of cardiac afterload without an increase in preload are perhaps of particular relevance to the treatment of patients with mild to moderate congestive heart failure.

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Usefulness of Adenosine in Augmenting Ventricular Preexcitation for Noninvasive Localization of Accessory Pathways

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Adenosine was administered to test the hypothesis that it would maximize preexcitation and facilitate noninvasive localization of accessory pathways in 22 patients with suspected accessory pathway–mediated tachycardias. Twelve-lead electrocardiograms and 2-dimensional echocardiograms were recorded at baseline and during adenosine-augmented ventricular preexcitation to localize the accessory pathway. Phase analysis was performed on digitized 4-chamber and short-axis views using a first harmonic Fourier transformation. At baseline, 15 patients had manifest preexcitation. In 14 of these patients (93.3%), preexcitation became more prominent after adenosine. Four patients without preexcitation at baseline clearly had it after adenosine. In patients who had preexcitation in response to adenosine, the electrocardiogram correctly identified the accessory pathway locations in 18 of 19 patients at a regional level and was incorrect in 1 of 19 patients. Echocardiographic phase analysis correctly identified the accessory pathway location in all 17 patients, who had technically adequate studies, at a regional level. In conclusion, administration of adenosine accentuates preexcitation, allowing for more accurate electrocardiographic and echocardiographic accessory pathway localization.

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Accurate noninvasive pathway localization is important in guiding appropriate use of catheter ablative techniques. Several noninvasive methods have been used in order to help localize accessory pathways with electrical or mechanical cues. These include 12-lead electrocardiograms using delta wave vector evaluation,[1] multilead surface electrocardiographic mapping,[2] and 2-dimensional echocardiographic imaging using inspection of digitized cine-loop,[3–5] or phase analysis of radionuclide blood pool scintigraphy[6–9] to localize the pathway via the sight of earliest motion. Atrial pacing augments the degree of preexcitation, facilitating accessory pathway localization by each of these methods.[10–15] Recently, Kuecherer et al[15] demonstrated the use of 2-dimensional echocardiographic phase analysis in conjunction with right atrial pacing to maximize preexcitation and facilitate pathway localization. Adenosine, an intravenous short-acting atrioventricular nodal blocking agent,[16–18] might be expected to facilitate anterograde bypass tract conduction without need for cardiac pacing. The purpose of our study was to test the hypothesis that adenosine augments preexcitation, thereby facilitating the noninvasive localization of accessory pathways. In this study, 3 noninvasive methods (12-lead electrocardiogram, 2-dimensional echocardiographic cine-loop inspection, and phase analysis) were evaluated at baseline and after adenosine infusion in patients with suspected accessory pathway–mediated tachycardias in order to determine their ability to localize the pathways.

METHODS

Study group: We prospectively studied 22 consecutive patients referred to the University of California San Francisco, for known or suspected accessory pathway–mediated tachycardias. Manifest preexcitation was defined as the presence of ventricular preexcitation on the 12-lead electrocardiogram (15 patients). In 7 other patients, an accessory pathway–mediated tachycardia was suspected since the 12-lead electrocardiogram during supraventricular tachycardia showed inscription of the P wave in the ST segment during tachycardia. All patients were in sinus rhythm at baseline and had normal left ventricular function. There were 11 men and 11 women (mean age 31 ± 3 years, range 13 to 67). This study was approved by the Institutional Review Board of the University of California San Francisco and each patient gave informed consent.

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Study protocol: Each patient was connected to a 12-lead electrocardiogram and intravenous access was obtained. A 2-dimensional echocardiogram was obtained in the left lateral decubitus position using standard equipment (Hewlett Packard 500 and 1000, Andover, Massachusetts). A parasternal short-axis view was obtained just below the atrioventricular groove to visualize the full circumference of right and left ventricular endocardium. In addition, a slightly posteriorly oriented apical 4-chamber view was obtained to assist in the triangulation of foci localization. These images were acquired at 16 to 20 cm display depths and sampling frequencies of 30 to 60 Hz. Images were recorded both on videotape and on-line in cine-loop format (16 frames per cycle) using Cine-View Plus ™ (Freeland Systems, Louisville, Colorado) by gating acquisition to the R-wave upstroke. Cine-loops were stored on high-density disks (960K bytes, 60K bytes per frame).

Twelve-lead electrocardiograms and 2-dimensional echocardiograms, in cine-loop format for qualitative analysis and phase image format for quantitative analysis, were simultaneously obtained during sinus rhythm and immediately after intravenous bolus injection of adenosine. Doses were given every 5 minutes as needed for complete echocardiographic data acquisition (maximum 5 doses per patient). The first 3 patients received 3 and 6 mg of adenosine. Subsequent patients received either 6 or 12 mg doses of adenosine. Echocardiograms were obtained by an observer unaware of the 12-lead electrocardiographic and electrophysiologic findings, not available at the time of study. Adenosine-augmented electrocardiograms and echocardiograms were read by independent observers unaware of clinical findings. These results were compared with those determined by invasive electrophysiologic mapping, confirmed in all but 1 case by successful catheter ablation.

Phase analysis: The on-line cine-loop visual images were mathematically transformed using customized first harmonic Fourier analysis algorithms.[19] The first harmonic curve was fitted to a time-intensity curve for each individual pixel on a 256 × 240 image matrix. In this curve, amplitude depends on changes in pixel intensity, and the phase angle is determined by the onset of intensity change of wall motion. Phase angles were then automatically color-coded.[20] The resultant color images coded the sequence and extent of motion of the endocardial surface and chamber walls during a complete cardiac cycle. The R wave of the surface electrocardiogram was taken as 0 degrees. The site of earliest ventricular motion was represented by the earliest phase angle. An eccentric ventricular activation sequence, not originating from normal anterograde atrioventricular nodal conduction, could then be determined. Because the first harmonic curve is essentially a cosine function, earliest epicardial phase angles are indicated by a decrease in intensity during inward wall motion. However, inward endocardial motion is represented by increasing intensity to adjacent cavitary regions and is identifiable by a phase shift of 180 degrees. Therefore, the endocardial focus localized by phase echocardiography, unlike scintigraphic localization, is earliest among endocardial sites but shifted 180 degrees. Normal maximal myocardial thickening and endocardial inward motion was visually recognized by phase angles encoded in purple and red shades. These corresponded to phase angles of >100 degrees. In contrast, accessory pathway insertions were detected by abnormally early phase angles, <50 degrees, and encoded in green color shades.

Data analysis: STANDARD 12-LEAD ELECTROCARDIOGRAM: Baseline and postadenosine (preexcited) 12-lead electrocardiograms were interpreted without knowledge of either the echocardiographic or electrophysiologic findings. Accessory pathway localization was determined by the delta wave vector as previously described.[1]

VISUAL INSPECTION OF TWO-DIMENSIONAL ECHOCARDIOGRAPHIC CINE-LOOP IMAGES: Baseline and postadenosine cine-loop images were also interpreted by another investigator without knowledge of the electrocardiogram or electrophysiologic findings. Two-chamber short-axis views at the atrioventricular groove were divided into the following segments as illustrated in Figure 1: (1) left anterior septal and left posterior septal, left anterior, left lateral and left posterior; and (2) right anterior, right lateral and right posterior. On the apical 4-chamber view left posterior, posteroseptal and right lateral segments were visualized for additional conformation.

VISUAL INSPECTION OF PHASE IMAGES: Color-coded phase images were analyzed for the site of earliest ven-

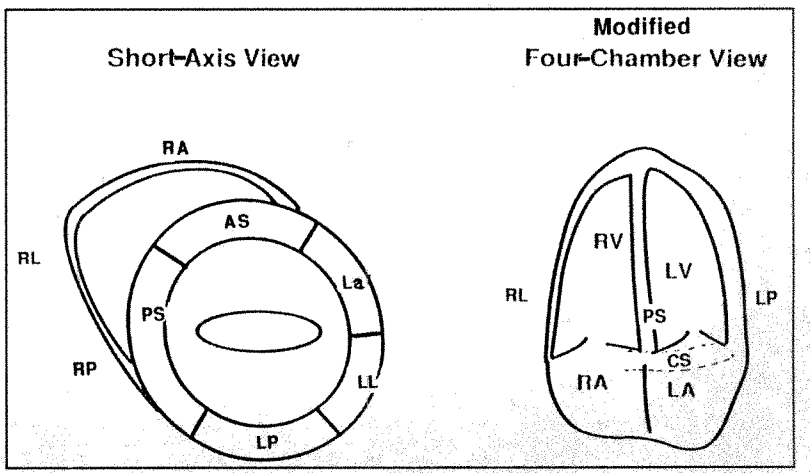


FIGURE 1. Representation of a 2-chamber short-axis view just below the atrioventricular groove, and a slightly posteriorly oriented apical 4-chamber view. In the modified 4-chamber view, segments were divided into right lateral (RL), left posterior (LP) and posteroseptal (PS). Eight segments were identified in the short-axis view: anteroseptal (AS), posteroseptal (PS), left anterior (La), left lateral (LL), left posterior (LP), right anterior (RA), right lateral (RL) and right posterior (RP). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

TABLE I Dose Response of Adenosine (n = 19)

Dose (mg)	Injections	Augmentation	Sensitivity (%)
3	6	0	0
6	21	16	76
12	45	45	100*
Totals	72	61	83

*p <0.001 (vs 3.0, 6.0 mg).

tricular endocardial phase angle in both short-axis and apical 4-chamber views by another investigator, without knowledge of echocardiographic, electrocardiographic or electrophysiologic findings. The same myocardial and endocardial segments were utilized for this method as previously described. Absolute phase angles for these sites were determined at baseline and after adenosine.

Blind assessment of accessory pathway presence and location: The identification of the bypass tract location was blindly scored for all methods (at baseline and after adenosine). The precise accessory pathway location was determined by endocardial mapping studies in all and confirmed by catheter ablation in all but 1 patient. For purposes of this study, identification of the pathway by noninvasive means was determined as regional localization, defined as correct localization to the involved or adjacent segments or segmental localization, where the correct segment was identified. All other localizations were classified as incorrect.

Statistical analysis: Baseline and postadenosine noninvasive localizations of accessory pathways were compared using contingency tables. Cochran's test was used to determine whether a significant difference existed between the various noninvasive methods. A p value <0.05 was considered statistically significant. All data are presented as mean ± standard error.

RESULTS

Endocardial mapping/catheter ablation: All 22 patients with suspected accessory pathway–mediated tachycardias subsequently underwent endocardial mapping to identify the pathway location: 19 patients had the Wolff-Parkinson-White syndrome, 3 had concealed accessory pathways, and none had bundle branch block; each patient had only a single pathway. In 21 of the 22 patients, localization was confirmed after successful catheter ablation at the following locations: posteroseptal (10 patients), left lateral (4 patients), left posterior free wall (3 patients), and right anterior (2 patients). Three patients had concealed anterograde conduction with accessory pathways in the left anterior, left posterior, and septal locations, which could not be assessed by noninvasive methods. The location as determined by endocardial mapping/ablation served as our reference against which the noninvasive methods were tested.

Dose response to adenosine: Seventy-eight intravenous adenosine bolus injections were administered to 22 patients in this study (2 to 5 injections per patient with a cumulative dose range of 12 to 60 mg/patient). A total of 72 injections were given to the 19 patients with proven anterograde accessory pathway conduction. Of these 72 injections, electrocardiographic preexcitation was augmented in none of the 6 intravenous injections of 3 mg, 16 of 21 injections (76%) of 6 mg, and each of 45 injections (100%) of 12 mg (Table I). At baseline, 15 patients had manifest electrocardiographic preexcitation. In 14 of 15 patients (93.3%) preexcitation became

TABLE II Pathway Localization in Patients with Accessory Pathway–Mediated Tachycardias

		Electrocardiogram		Cine-Loop		Echocardiographic Phase	
Pt.	EPS	Baseline	Adenosine	Baseline	Adenosine	Baseline	Adenosine
1	Posteroseptal	*Normal*	Posteroseptal	*Normal*	*Left lateral*	Posteroseptal	Posteroseptal
2	Posteroseptal	Posteroseptal	Posteroseptal	*Normal*	Posteroseptal	*Normal*	Posteroseptal
3	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal
4	Posteroseptal	*Normal*	Posteroseptal	*Normal*	Posteroseptal	*Normal*	Posteroseptal
5	Posteroseptal	Posteroseptal	Posteroseptal	*Normal*	Posteroseptal	*Normal*	Posteroseptal
7	Posteroseptal	*Right posterior*	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal
13	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal	Posteroseptal
15	Posteroseptal	Posteroseptal	Posteroseptal	*Normal*	Posteroseptal	*Normal*	Posteroseptal
18	Posteroseptal	Posteroseptal	Posteroseptal	*Normal*	Posteroseptal	*Normal*	Posteroseptal
22	Posteroseptal	*Normal*	Posteroseptal	*Normal*	Posteroseptal	*Normal*	Posteroseptal
6	Left lateral	Left lateral	Left lateral	*Normal*	*Posteroseptal*	Left lateral	Left lateral
11	Left lateral	Left lateral	Left lateral	*	*	*	*
14	Left lateral	Left lateral	Left lateral	*Normal*	Left lateral	*Normal*	Left lateral
16	Left lateral	*Left posterior*	*Posteroseptal*	*Normal*	Left lateral	*Normal*	Left lateral
8	Left posterior	Left posterior	Left posterior	*Normal*	Left posterior	Left posterior	Left posterior
9	Left posterior	Left posterior	Left posterior	*	*	*	*
12	Left posterior	*Posteroseptal*	Left posterior/ posteroseptal	*Normal*	*Posteroseptal*	*Posteroseptal*	Left posterior/ posteroseptal
21	Right anterior	*Normal*	Right anterior	Right anterior	Right anterior	Right anterior	Right anterior
10	Right anterior	Anteroseptal/ right anterior	Anteroseptal/ right anterior	*Normal*	Right anterior	Anteroseptal/ right anterior	Anteroseptal/ right anterior
17	Left anterior (c)	Normal	Normal	Normal	Normal	Normal	Normal
19	Septal (c)	Normal	Normal	Normal	Normal	Normal	Normal
20	Left posterior (c)	Normal	Normal	Normal	Normal	Normal	Normal

*Technically inadequate images for cine-loop and echo-phase analysis; indeterminant prediction of accessory pathway location is shown in *italics*.
(c) = concealed pathway; EPS = electrophysiology study.

more "prominent" after administration of adenosine. Adenosine administration resulted in manifest preexcitation in 4 of 7 patients with normal baseline electrocardiograms. The baseline QRS duration was 115 ± 5 ms and increased after adenosine infusion to 155 ± 5 ms ($p > 0.001$).

The procedure was tolerated in all patients, each experiencing transient mild discomfort, facial flushing, paresthesia and dyspnea. Patient 18, a 16-year-old woman, had transient T-wave inversion without chest pain immediately after 12 mg of adenosine which promptly resolved within 1 minute. Patient 19, who was being treated with verapamil and atenolol, had an asymptomatic 3.2-second sinus pause.

Noninvasive localization of accessory pathways before and after adenosine: Table II lists the detailed predicted accessory pathway locations in each of the patients by the various methods. Table III lists the overall results of these noninvasive methods (in total) predicting pathway location. Localization by 12-lead electrocardiogram at baseline was correct at a regional level in 15 of 19 patients, correct at a segmental level in 11 of 19 patients, and incorrect in 3 of 19 patients. In patients with ventricular preexcitation after adenosine, the electrocardiogram correctly identified the accessory pathway location in 18 of 19 patients on a regional level, in 16 of 19 patients at a segmental level and was incorrect in only 1 patient. Adenosine administration resulted in manifest preexcitation in 4 of the 7 patients with normal baseline electrocardiograms (Figures 2 and 3). Three patients had no evidence of preexcitation after adenosine (60 mg total per patient). Each of these patients had a concealed accessory pathway at electrophysiologic study.

Visual inspection of the cine-loop 2-dimensional echocardiogram before adenosine could correctly local-

TABLE III Adenosine Localization of Accessory Pathways (n = 19)

	Correct		
	Segmental	Regional	Incorrect
ECG			
Baseline	11*	15	3
Adenosine	16†	18‡	1
2-D cine-loop			
Baseline	3	3	15
Adenosine	14†	14†	5
Phase analysis			
Baseline	7	10	8
Adenosine	15†	17†	2

*$p < 0.001$ (baseline ECG vs 2-dimensional cine-loop); †$p < 0.05$ (baseline vs adenosine); ‡$p < 0.05$ (adenosine ECG vs adenosine 2-dimensional cine-loop).
ECG = electrocardiogram; 2-D = 2-dimensional.

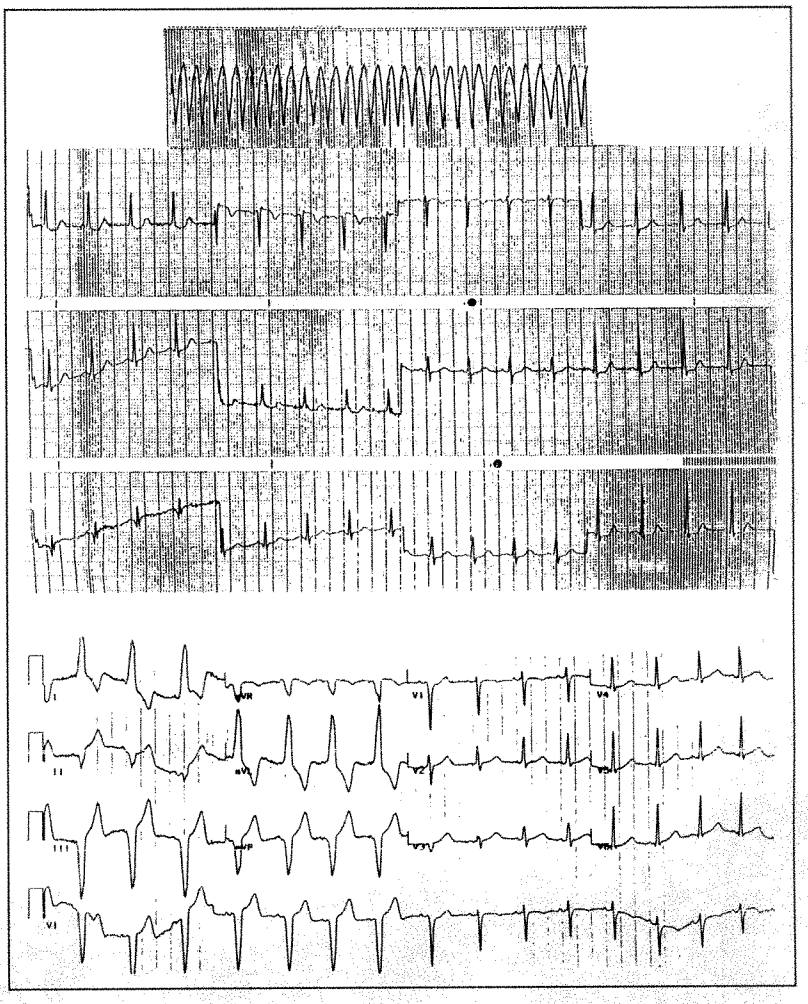


FIGURE 2. ***Top, upper strip*** **shows wide complex tachycardia in patient 21, with a regular ventricular rate of 300 beats/min. Tachycardia was terminated by vagal maneuvers. Baseline electrocardiogram** ***(bottom panel)*** **was interpreted as normal. After a single injection of 12 mg of adenosine, preexcitation was recoded confirming the diagnosis of Wolff-Parkinson-White syndrome** ***(bottom).*** **This electrocardiogram demonstrates the transient nature of adenosine, and the necessity of recording all 12 leads simultaneously. The pattern was blindly interpreted as a right anterior accessory pathway, later proven by successful radiofrequency catheter ablation.**

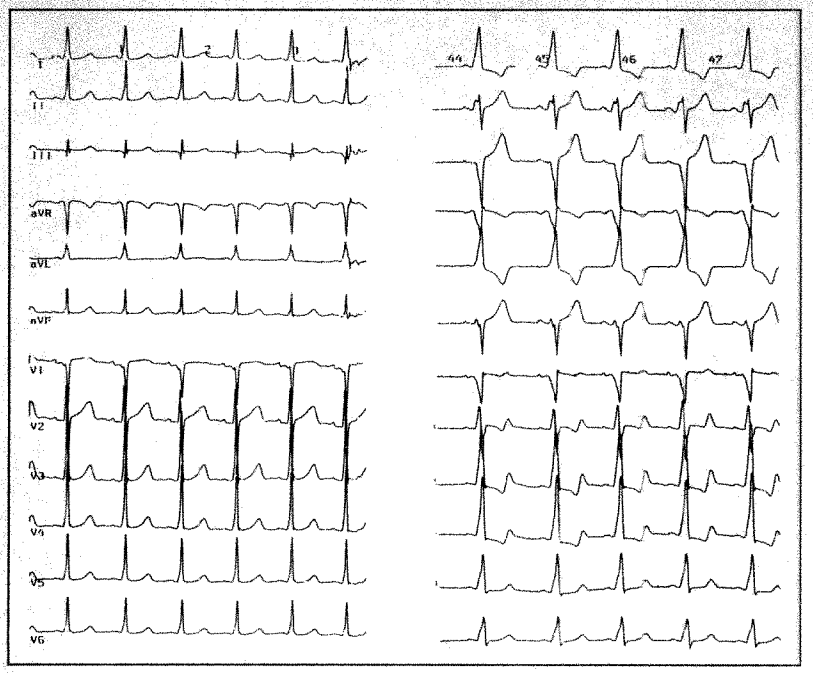


FIGURE 3. Baseline *(left)* and postadenosine *(right)* 12-lead electrocardiograms in patient 22. After adenosine, preexcitation was identified and the pathway was localized correctly by each of our noninvasive methods to a posteroseptal location.

ize only 3 of 19 pathways. However, after adenosine, localization was correct at the regional and segmental level in 14 of 19 patients and incorrect in only 5 of 19 patients ($p < 0.05$).

All patients with accessory pathways showing anterograde conduction, including those with posteroseptal pathways, were distinguishable from those with normal atrioventricular conduction. The mean baseline phase angle was 97 ± 14 degrees (range 17 to 156). After adenosine, a wall motion abnormality was observed immediately after the R wave with a mean phase angle of 10 ± 3 degrees (range −11 to 35). Therefore, a significant phase angle shift was seen in patients with ventricular preexcitation ($p < 0.001$). Figure 4 shows the measured phase angles of the earliest activation sequence for all patients before and after adenosine. Inspection of 2-dimensional echocardiographic phase images after adenosine correctly identified 17 of 19 patients at a regional level compared with 10 of 19 at baseline ($p < 0.05$), and 15 of 19 patients at a segmental level compared with 7 of 19 at baseline ($p < 0.05$). Figure 5 shows short axis phase images in patient 6. This patient had a normal baseline phase image, and after adenosine a left lateral phase angle shift was noted in the segment correctly identifying the accessory pathway insertion to this area. Figure 6 shows similar phase images in patient 7 who had a posteroseptal pathway.

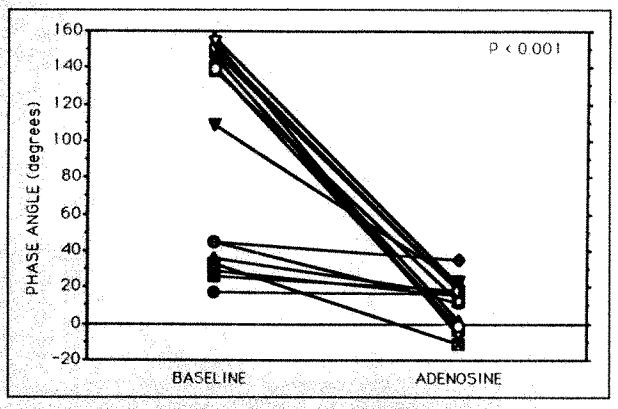


FIGURE 4. Measured phase angles of the earliest activation sequence at baseline and after adenosine in patients with anterograde accessory pathway conduction. A significant phase angle shift was observed ($p < 0.001$).

Two cases (patients 1 and 6) incorrectly identified by echocardiographic cine-loop inspection were correctly identified by 12-lead electrocardiogram and echocardiographic phase analysis after adenosine augmentation. Two cases (patients 9 and 11) were correctly identified by adenosine electrocardiogram interpretation but not by echocardiographic means (cine-loop and phase analysis) because of technically inadequate images. One case (patient 16) was correctly localized by both echocardiographic techniques after adenosine administration but incorrectly localized by 12-lead electrocardiogram. When technically adequate images were obtained, echocardiographic phase analysis correctly localized the accessory pathway insertion in all cases.

DISCUSSION

Adenosine is a potent atrioventricular nodal blocking agent with a short half-life.[16–18] This medication has been shown to be very effective for terminating supraventricular tachycardias.[21–24] Recently, Garratt et al[25] gave intravenous adenosine to 22 patients with supraventricular tachycardia and normal electrocardiograms and were able to unmask latent preexcitation in 4 of these patients.

Previously, Kuecherer et al[15] at our institution compared electrocardiographic and echocardiographic analysis for pathway location using right atrial pacing to augment ventricular preexcitation. Their results differed from those observed in our study in that a lower percentage of correct electrocardiographic localizations were observed. This may be explained by a different

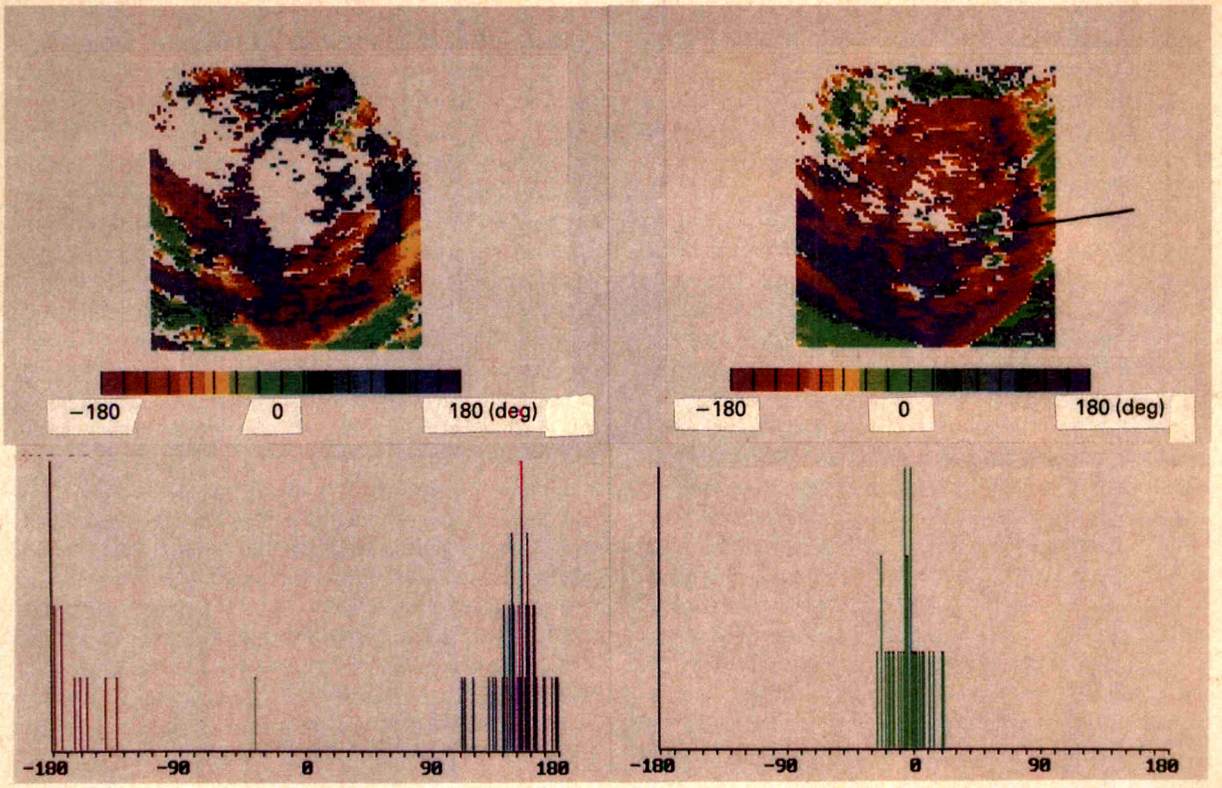


FIGURE 5. Phase images obtained from the short-axis view in patient 6. By convention, phase angles were measured in areas that corresponded to maximal inward motion of the endocardium during systole. Phase images obtained at baseline *(left)* demonstrated normal phase angles (nearly identical to motion of the interventricular septum and posterolateral wall). Images obtained approximately 20 seconds after bolus injection of 12 mg of adenosine *(right)* demonstrated a markedly abnormal phase angle *(green, as indicated by arrow)* in the left lateral distribution. Therefore, a left lateral pathway was identified.

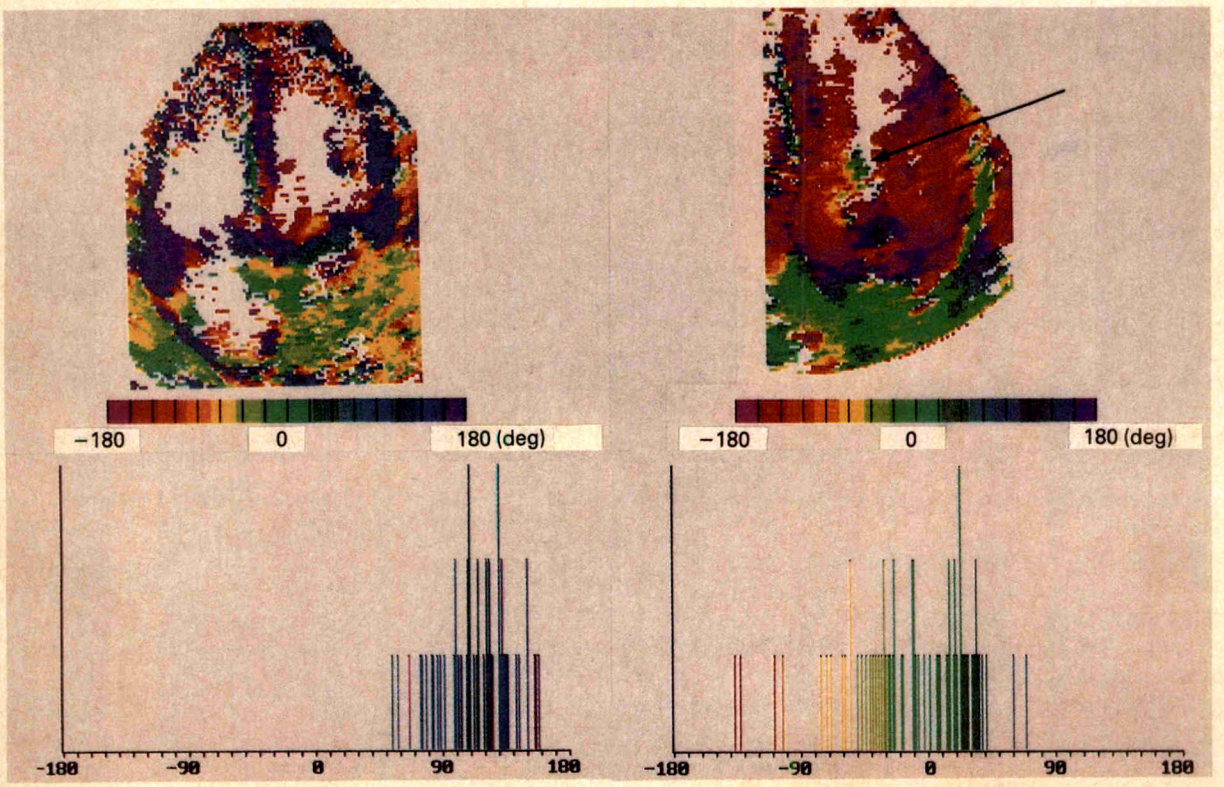


FIGURE 6. Phase image (4-chamber view) in patient 7. This patient had a normal baseline phase image *(left)*. After administration of adenosine *(right)*, a markedly abnormal phase angle *(green, as indicated by arrow)* was localized to the posteroseptal region, which correctly identified the accessory pathway location.

method of augmenting preexcitation or a different distribution of accessory pathway localizations (by chance) that included patients with anteroseptal and intermediate septal pathways which may be impossible to separate by analysis of electrocardiograms. Such patients were not observed in our study.

We used adenosine to augment ventricular preexcitation in an attempt to improve noninvasive accessory pathway localization. We found that adenosine-augmented electrocardiographic and echocardiographic phase analysis proved the most successful. Echocardiographic cine-loop and phase-imaging techniques required more complex equipment (2-dimensional echocardiograms and customized computer equipment), were more time consuming, and limited by the need for studies of suitable technical quality.

Segmental localization improved after adenosine by all methods when compared with baseline. The modified 4-chamber view did not correctly identify any additional pathways than those identified by short-axis view cine-loop. Adenosine-augmented phase analysis identified all accessory pathways at the regional level in patients with technically adequate echocardiographic images. Adenosine-augmented 12-lead electrocardiograms were significantly better than adenosine cine-loop inspection at the regional but not segmental level. There were no significant differences between adenosine augmented 12-lead electrocardiographic and phase analysis.

The goal of electrocardiographic and echocardiographic localization was precise segmental accessory pathway localization. Overall, in approximately 79% of cases, segmental localization was achieved after adenosine (electrocardiogram 84%, cine-loop 74%, phase analysis 79%). This improved to approximately 86% with a less precise regional localization (electrocardiogram 95%, cine-loop 74%, phase analysis 89%). Regional localization might be useful in selecting the appropriate approach (right or left side) for the ablative procedure.

Four of 19 patients with anterograde accessory pathways had normal baseline 12-lead electrocardiograms, and had preexcitation after adenosine. These pathway locations were posteroseptal in 3 and right anterior in 1 patient. This was unexpected, since baseline preexcitation is usually observed with these locations because of their proximity to the atrioventricular node. Although the mechanism for these observations is unclear, it may be partly related to the fact that preexcitation may be obscured in the presence of rapid atrioventricular nodal conduction.

Both 6 and 12 mg adenosine doses were well tolerated by all patients and appear to be safe and effective in augmenting preexcitation in the baseline state. However, adenosine has the potential to precipitate atrial fibrillation, possibly due to shortening of the atrial refractory period. After completion of this study, we observed adenosine-induced atrial fibrillation in a patient with Wolff-Parkinson-White syndrome and a history of recurrent spontaneous atrial fibrillation.

The techniques used in this study have several limitations. First, adenosine electrocardiographic analysis was incapable of precise localization at the segmental level in 3 of 19 patients. This may be due to the fact that delta wave vectors are obtained from body surface recordings and are dependent on myocardial orientation as well as thoracic dimensions and configurations. Second, the short half-life of adenosine requires rapid electrocardiographic and echocardiographic acquisition, potentially compromising echocardiographic image quality. Therefore, multiple boluses were necessary to produce optimal echocardiographic images that corresponded with peak electrophysiologic effect. Third, echocardiographic cine-loop inspection and phase analysis were dependent on the quality of echocardiographic images. In 2 cases, satisfactory echocardiographic studies could not be obtained. Fourth, the right ventricular endocardium is more difficult to image than the left ventricle, and thus a higher incidence of errors for right-sided pathways by echocardiography might be anticipated. As expected, adenosine had no effect in patients with concealed accessory pathways, and therefore their studies were indistinguishable from normal subjects by all methods. Finally, in rare instances, conduction over accessory pathways may be blocked by purinergic compounds.[26] Therefore, this test may not be universally applicable.

In conclusion, administration of adenosine accentuates preexcitation, allowing for more accurate electrocardiographic and echocardiographic accessory pathway localization.

Acknowledgment: We gratefully acknowledge Elan D. Scheinman, BA, for help in the development of the phase analysis software.

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Differences Between Predictive Characteristics of Signal-Averaged Electrocardiographic Variables for Postinfarction Sudden Death and Ventricular Tachycardia

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Several studies indicate that the electrophysiologic substrate for sustained ventricular tachycardia differs from that of ventricular fibrillation. This prospective study examined whether there were clinically relevant differences between the predictive values of the standard time-domain signal-averaged (SA) electrocardiographic (ECG) variables for ventricular tachycardia and sudden death after myocardial infarction. Predischarge SA electrocardiograms were recorded in 332 patients after infarction. During a follow-up period of ≥6 months, there were 12 sudden deaths (3.6%), 14 patients (4.2%) developed spontaneous sustained ventricular tachycardia and 20 patients (6%) died of circulatory failure. The sensitivity, specificity and positive predictive accuracy of the numerical values of the time-domain SA electrocardiographic variables for predicting sudden death and ventricular tachycardia were compared. The optimal criteria for predicting ventricular tachycardia required the positivity of ≥2 of the standard time-domain SA variables, whereas the optimal criteria for predicting sudden death required the positivity of all 3 variables. A high specificity was sustained over a wider range of sensitivity for sudden death than it was for ventricular tachycardia and the values of the variables which provided the same sensitivity for sudden death and ventricular tachycardia were different. For a sensitivity of 70%, the positive predictive accuracy was 31% for predicting sudden death and 13% for predicting ventricular tachycardia. The study concludes that differences in the predictive characteristics of variables for ventricular tachycardia and sudden death may be used to refine postinfarction risk stratification.

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"Late potentials" on the signal-averaged (SA) electrocardiogram (ECG) are associated with an increased risk of arrhythmic events after myocardial infarction.[1,2] However, the SA ECG has several limitations when applied to postinfarction risk stratification. Some workers have diagnosed late potentials with reference to normal control subjects,[3] whereas others have used criteria that were derived from patients with a history of ventricular tachycardia.[4] Second, the categorical criteria used for diagnosing late potentials cannot be adjusted to provide the predictive characteristics that would best suit all clinical situations. Finally, the term "arrhythmic events," embraces both sustained ventricular tachycardia and sudden death, which are end points with different clinical implications.[5] Recent studies have shown that the electrophysiologic substrate in patients presenting with hemodynamically stable sustained ventricular tachycardia may differ from that in patients who present with cardiac arrest.[6–8] Therefore, postinfarction risk stratification could be substantially refined if, by using the numerical values of the time-domain the SA electrocardiographic variables to describe the electrophysiologic substrate, the risks of sudden death and sustained ventricular tachycardia could be individually assessed. We therefore examined whether there are important differences between the predictive values of the standard time-domain SA electrocardiographic variables for sudden death and ventricular tachycardia after myocardial infarction.

METHODS

Patient population: The eligible patient population consisted of 379 patients admitted to the hospital with acute myocardial infarction. Acute myocardial infarction was defined by standard criteria. Forty-five patients with atrial fibrillation, important noncardiac disease, a history of previous cardiac surgery or permanent pacemaker insertion and patients with bundle branch block or ventricular preexcitation were excluded because these conditions complicate time-domain analysis of the SA ECG. Therefore the study population consisted of 332 patients aged 26 to 74 years (mean 56.7 ± 9). The site of infarction was anterior in 168 patients, inferior in 156 and indeterminate in 8. Of the 332 patients, 40 (12.1%)

had had a previous myocardial infarction, 133 (40%) were discharged taking β-blockers, and 149 (45%) received streptokinase and aspirin during the acute infarction. Specific prophylactic antiarrhythmic therapy was not routinely prescribed and patients later presenting with ventricular tachycardia were treated as deemed appropriate by the attending cardiologist.

Data recordings: A high-gain SA ECG was recorded in each patient between the sixth and eleventh day after admission using a system of Arrhythmia Research Technology, model 1200 EPX. The system uses frank orthogonal leads and a sampling rate of 1 KHz. Low- and high-pass filter settings of 250 and 25 Hz, respectively, were used. A noise level of <0.3 uV was achieved in 70% of the patients and a noise level of <0.5 uV in the remaining patients. The following variables were computed: the total duration of the filtered QRS complex, the root-mean-square voltage of the terminal 40 ms of the averaged QRS complex, and the duration of the terminal signals lower than 40 mV, namely, the low-amplitude signal duration. No patient took specific antiarrhythmic therapy during SA electrocardiographic recording.

Normal ranges for the SA variables were based on the results of recordings undertaken in 60 control subjects (45 men aged 24 to 90 years, mean 54) with no evidence of heart disease. The total duration of the filtered QRS complex ranged from 77 to 139 ms (mean 99 ± 13), low-amplitude signal duration from 8 to 55 ms (mean 25 ± 8.4), and root-mean-square voltage of the terminal 40 ms from 15.0 to 186 (mean 67.5 ± 44): 97% of the patients had tQRS <118 ms, low-amplitude signal duration <36 ms and root-mean-square >19, and these values were used to delimit a normal SA ECG.

Left ventricular ejection fraction was assessed by radionuclide angiography or contrast angiography within a month of infarction.

Risk stratification: The major end points of sudden death and ventricular tachycardia were classified by a group of physicians without knowledge of the risk stratification results. As in the Cardiac Arrhythmia Pilot Study,[9] sudden death was defined as death within an hour of the onset of new symptoms: sudden death also included instantaneous deaths and those who died in their sleep as well as those whose death was unwitnessed but occurred within an hour of last being seen alive. Sustained ventricular tachycardia was defined as spontaneous electrocardiographically documented symptomatic ventricular tachycardia lasting for ≥30 seconds.

Comparisons between the predictive characteristics of the SA electrocardiographic variables were obtained by using receiver-operator characteristic curves, which describe the dependence of specificity on sensitivity. They were plotted from the highest values of specificity calculated for each value of sensitivity. Three different diagnostic approaches were used, diagnosing a pathologic result of the time-domain SA electrocardiographic analysis when ≥1, ≥2, or all 3 of the variables had abnormal values. The values of the SA electrocardiographic variables in patients who developed events were selected as dichotomy points. Values of total filtered QRS duration or low-amplitude signal duration which were higher, and values of the root-mean-square voltage of the last 40 ms of the filtered QRS complex which were lower, than the selected dichotomy point were defined as abnormal. For each value of sensitivity, all combinations of dichotomy points of the SA electrocardiographic variables were examined and specificity was calculated from the corresponding counts of true-negative cases. Receiver-operator characteristic curves were then plotted.[10]

TABLE I Clinical Characteristics of Patients with Ventricular Tachycardia and Sudden Death

	Spontaneous VT	Sudden Death
No. of pts.	14	12
Mean age (yr)	60	59
Mean LVEF (%)	38	48
LVEF <40%	7	7
Time to event <90 days	9	7
Streptokinase	6	4
Previous AMI	2	2

AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction; VT = ventricular tachycardia.

Statistics: The standard unpaired *t* test assuming the same variances of the analyzed samples was used to compare the numerical values of individual variables in the total patient population and for comparisons between the different patients subgroups, namely, (1) sudden death, (2) nonsudden deaths, (3) the group with sustained ventricular tachycardia, and (4) those who had no complications during follow-up.

The positive predictive accuracies of identification of the sudden death group and the ventricular tachycardia group by diagnostic approaches requiring ≥2 and all 3 variables were also compared. First the positive predictive accuracies for each of these diagnostic approaches were calculated for sensitivities of approximately 40, 50, 60 and 70%. Then, the proportion of true and false positive cases obtained when predicting sudden death was compared with the proportion of true and false positive cases obtained when predicting ventricular tachycardia using Fisher's complete test.

RESULTS

During a follow-up period of ≥6 months (183 to 1,616 days) 12 patients (3.6%) died suddenly, 20 (6%) died of circulatory failure, and 14 patients (4.2%) developed spontaneous sustained ventricular tachycardia. Table I compares the clinical characteristics of the patients who developed ventricular tachycardia with those who died suddenly. Between the 2 groups of patients there were no significant differences in age, proportion of patients with left ventricular ejection fraction <40%, mean left ventricular ejection fraction, proportion who received streptokinase or had a previous myocardial infarction, or the time to event.

In the complete patient population the values of root-mean-square voltage of the terminal 40 ms ranged from 4.9 to 285 μV, the total duration of the filtered QRS ranged from 54 to 206 ms; and the low amplitude signal duration ranged from 5 to 106 ms. Table II compares mean values and variances of the individual SA

electrocardiographic variables in the various patient groups. There was a significant difference in root-mean-square voltage, filtered QRS duration and low-amplitude signal duration between patients who died suddenly and and nonsuddenly, but not between patients who died suddenly and those who developed ventricular tachycardia: mean difference (+95% confidence limits) between the 2 groups for root-mean-square voltage was 0.3 ± 20 μV, for QRS duration 9 ± 17 ms and for low-amplitude signal duration 7 ± 13 ms (unpaired *t* test).

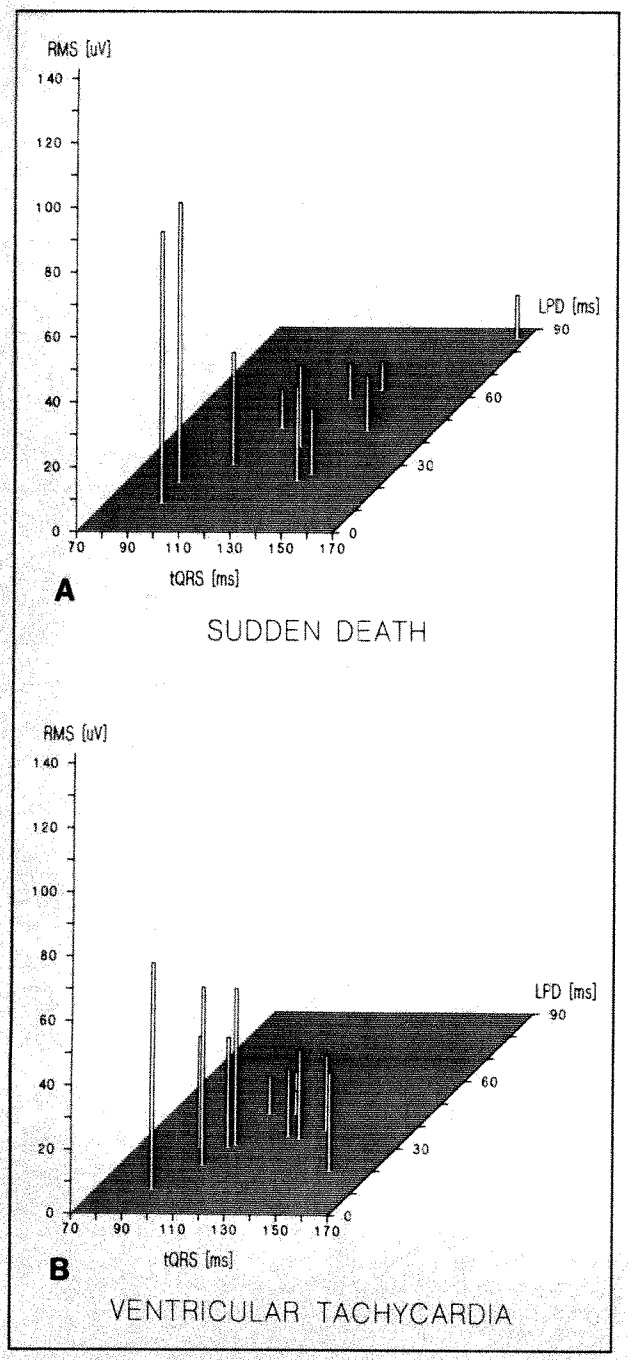
The distribution of the events in relation to the values of the SA electrocardiographic variables are seen in Figure 1. Sudden and nonsudden deaths are clustered at opposite poles of the figure, with the patients who developed ventricular tachycardia in between.

Characteristics curves: SENSITIVITY AND SPECIFICITY: The receiver-operator characteristic curves of the stratification of arrhythmic events, sudden death, ventricular tachycardia, all-cause mortality and nonsudden death are represented in Figure 2. A strategy requiring positivity of any 2 SA electrocardiographic variables provid-

TABLE II Mean ± Standard Deviation of Values of Signal-Averaged Electrocardiographic Variables in Patient Subgroups

	No. of Pts.	RMS (40 ms)	tQRS	LASD (40 ms)
SD	12	29 ± 28	124 ± 22	41 ± 21
VT	14	28 ± 19	116 ± 17	21 ± 12
p value		NS	NS	NS
SD	12	29 ± 28	124 ± 22	41 ± 21
NSD	18	51 ± 37	102 ± 15	23.0 ± 11.0
p value		NS	<0.006	<0.013
SD	12	29 ± 28	124 ± 22	41 ± 21
No events	288	69 ± 52	102 ± 17	25 ± 12
p value		<0.0001	<0.005	<0.02
VT	14	28 ± 19	116 ± 17	21 ± 11
NSD	18	51 ± 37	102 ± 15	11.0 ± 3
p value		<0.035	<0.02	<0.009
NSD	18	51 ± 37	102 ± 15	11 ± 3
No events	288	69 ± 52	102 ± 17	25 ± 12
p value		NS	NS	NS
Controls	60	68 ± 44	99.0 ± 13	25 ± 8
No events	288	69 ± 52	102 ± 17	25 ± 12
p value		NS	NS	NS

The p value was calculated by using the 2-sample *t* test.
LASD = Low-amplitude signal duration; No events = patients without events; NS = not significant; NSD = nonsudden death; RMS = root-mean-square; SD = sudden death; VT = ventricular tachycardia.



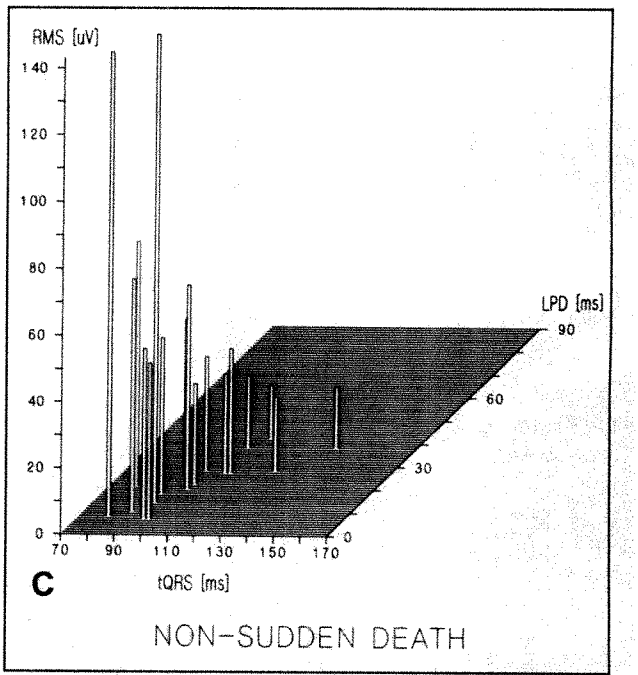
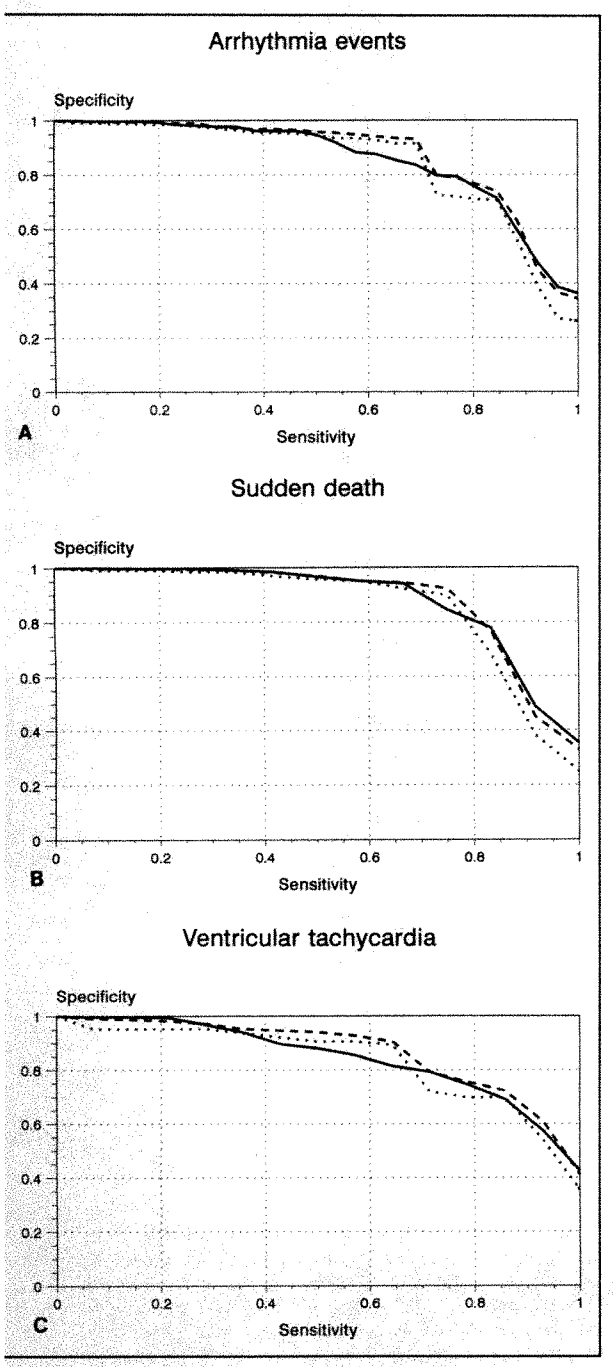


FIGURE 1. Three-dimensional representation of the numerical values of the standard time-domain signal-averaged electrocardiographic variables in sudden death *(A)*, ventricular tachycardia *(B)* and nonsudden death *(C)* groups. Sudden and nonsudden deaths are clustered at opposite poles of the figure, and patients with ventricular tachycardia lie between. LPD = low-amplitude duration; RMS = root-mean-square voltage.

ed the optimal curves for predicting arrhythmic events in general and ventricular tachycardia in particular.

For predicting sudden death, the strategy requiring positivity of all 3 variables performed similarly to that requiring any 2 variables when comparing the plots of specificity against sensitivity. The approach requiring the positivity of all 3 variables also performed better than that requiring the positivity of any 2 SA electrocardiographic variables when comparing the plots of positive predictive accuracy, particularly when sensitivity lay between 20 and 30%. A high specificity was sustained over a wider range of sensitivity for sudden death (Figure 2B) than it is for ventricular tachycardia (Fig 2C). Figure 2B and E, show that specificity was much higher and sustained at a higher level over a wider range of sensitivity for sudden than for nonsudden death.

SENSITIVITY AND POSITIVE PREDICTIVE ACCURACY: The dependence of positive predictive accuracy on sensitivity for the SA electrocardiographic variables used for stratification of arrhythmic events, sudden death, ventricular tachycardia all-cause cardiac mortality and nonsudden death are represented by Figure 3. The optimal approach for predicting arrhythmic events required the positivity of 2 variables. The optimal approach for predicting sudden death was provided by the positivity of all 3 variables. For predicting ventricular tachycardia, the highest positive predictive accuracy was provided by the positivity of all 3 variables for values of sensitivity between 10 and 30%. However, positive predictive accuracy was higher for sudden death than for ventricular tachycardia for nearly all values of sensitivity. Furthermore, the values of the SA electrocardiographic variables that provided the same sensitivity for sudden death and ventricular tachycardia were different (Table III). Statistical examination also showed some significant differences between the positive predictive accuracies of the sudden death and ventricular tachycardia predictions (Table IV).



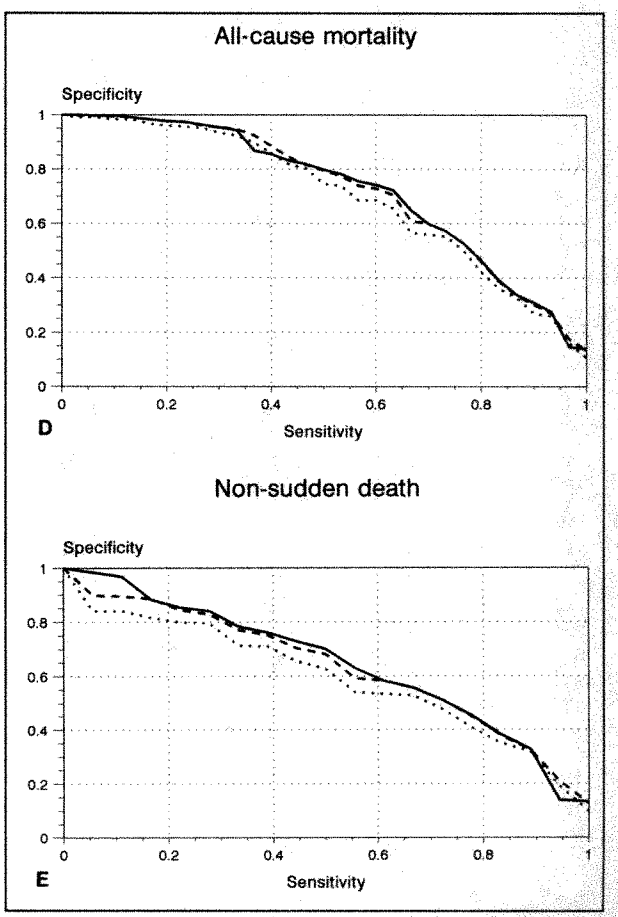


FIGURE 2. The receiver-operator characteristic curves for predicting arrhythmic events, sudden death, ventricular tachycardia, all-cause mortality and nonsudden death from the signal-averaged electrocardiographic variables. *Dotted line* corresponds to the criterion requiring the positivity of any 1 variable; *dashed line*, any 2 variables positive; *solid line*, all 3 variables positive.

The predictive characteristic of the SA electrocardiographic variables were better for sudden than nonsudden death, for which the positive predictive accuracy was about 10% across the whole range of sensitivity. This indicates that the SA electrocardiographic variables were unhelpful in predicting nonsudden death.

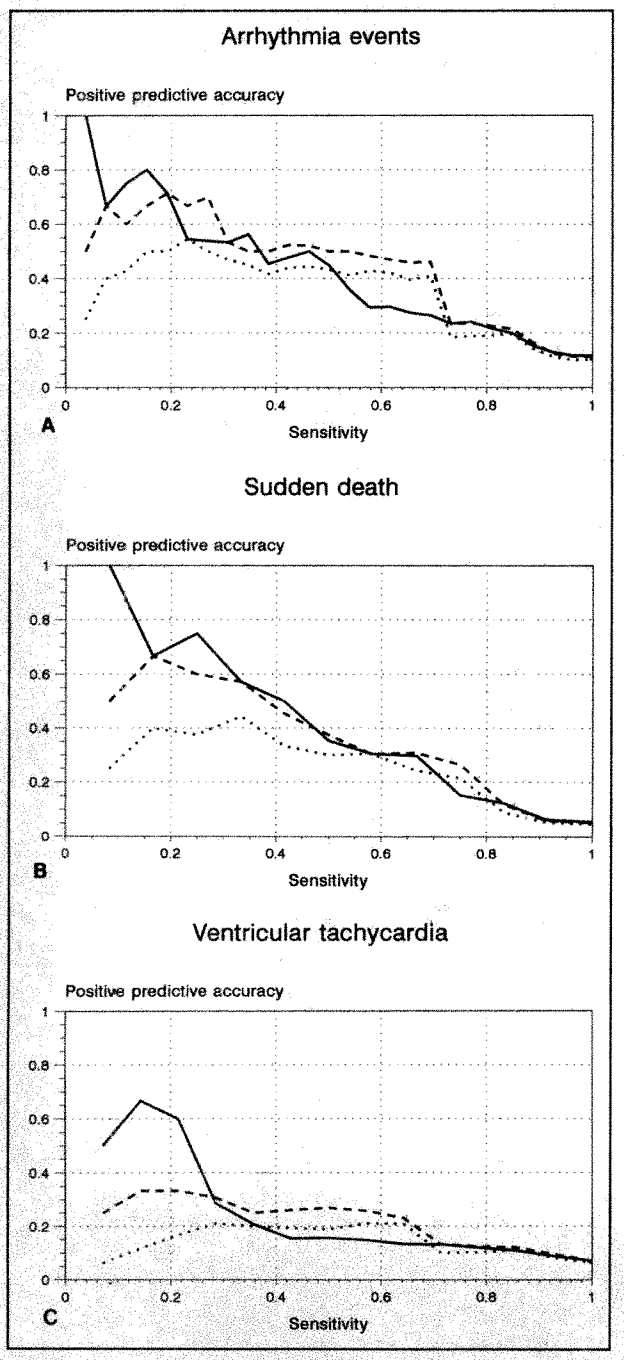
DISCUSSION

Study results: Ventricular activation time in sinus rhythm is significantly longer in animals with inducible ventricular tachycardia than in those with inducible ventricular fibrillation.[6–8] Similar findings have been reported in clinical studies based on the SA ECG.[11,12] Freedman et al[11] found that root-mean-square voltage of the last 40 ms of the filtered QRS was lower in pa-

TABLE III Criteria for Optimal Prediction of Ventricular Tachycardia and Sudden Death Using Signal-Averaged Electrocardiographic Variables

Sensitivity (%)	Limits for Maximal PPA: RMS (<=)	tQRS (>=)	LPD (>=)
Stratification of Ventricular Tachycardia: Two of Three Present			
40	7.1	124	34
50	8.2	124	34
60	11.8	124	34
70	11.8	105	30
Stratification of Sudden Death: Three of Three Present			
40	16.9	122	45
50	20.1	122	26
60	25.0	122	26
70	28.9	122	23

The values listed are only a few of several possible combinations of signal-average electrocardiographic values that gave the same predictive values. The dichotomy limits presented in the 2 parts of the table cannot be easily compared because they were derived using different diagnostic approaches.
LPD = low-amplitude signal duration; PPA = positive predictive accuracy; RMS = root-mean-square voltage.



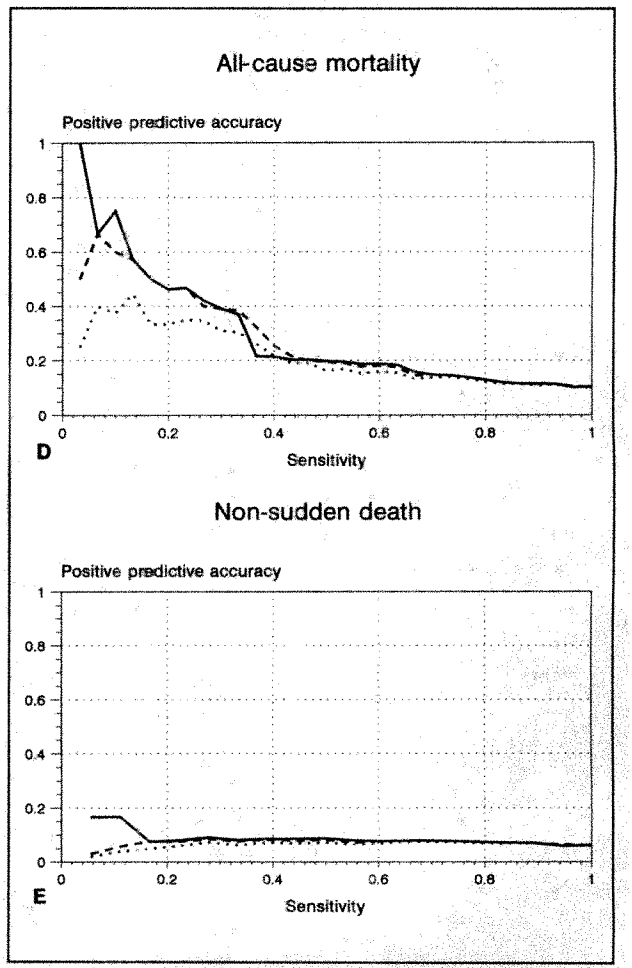


FIGURE 3. Sensitivity and positive predictive accuracy for predicting arrhythmic events, sudden death, ventricular tachycardia, all-cause mortality and nonsudden death from the signal-averaged electrocardiographic variables. The values of positive predictive accuracy are those that correspond to the maximal specificity. Explanation of symbols as in Figure 2.

tients with a history of ventricular tachycardia than in patients with a history of ventricular fibrillation. However, this study involved patients with various forms of structural heart disease and its results may not therefore be broadly applicable to patients with coronary artery disease. In a subsequent study of 65 patients presenting late after myocardial infarction, Denniss et al[12] found that the mean ventricular activation time was longer in patients with a history of ventricular tachycardia than in those presenting with ventricular fibrillation. They also found, as in previous studies,[13-15] that the mean cycle length of inducible ventricular tachycardia in the remaining patients was shorter in patients presenting with ventricular fibrillation than in those with a history of ventricular tachycardia. The lower the ejection fraction in these patients, the longer the cycle length of inducible tachycardia. Based on these findings, Denniss et al[12] suggested that markedly delayed ventricular conduction was a reflection of extensive myocardial scarring, and that this scarring resulted in a potential circuit too large to support the rapid rates at which ventricular tachycardia was likely to deteriorate into ventricular fibrillation. However, whether the SA ECG could distinguish patients with a history of ventricular fibrillation from otherwise comparable postinfarction patients without arrhythmias was not examined.[12] In their previous study, Freedman and colleagues[11] found no difference in root-mean-square voltage between normal control subjects and patients presenting with ventricular fibrillation.

The implications of these findings for the prospective risk stratification of postinfarction patients have not been addressed. Unlike Denniss et al,[12] we found no differences in the mean values of the SA electrocardiographic variables between patients who died suddenly and those who developed ventricular tachycardia, probably because of the small number of events. However, in the study of Denniss et al[12] the SA ECG recordings were recorded in patients with a history of an arrhythmic event, whereas the present study was prospective.

Nevertheless, we have found clinically important differences between the predictive characteristics of the SA electrocardiographic variables for sudden death and ventricular tachycardia (Figure 2). By comparison, categorical criteria based on our normal population gave a sensitivity of 65%, a specificity of 83%, but a positive predictive accuracy of only 12% for sudden death and a sensitivity of 76%, a specificity of 81% and a positive predictive accuracy of 15% for ventricular tachycardia. Simson's criteria[4] in the same patients gave a sensitivity of 62%, a specificity of 78% and a positive predictive accuracy of only 10% for sudden death, and a sensitivity of 75%, a specificity of 78% and a positive predictive accuracy of 13% for ventricular tachycardia.

Study limitations: One of the limitations of our study is the potentially erroneous assumption that all sudden deaths were due to ventricular fibrillation. Furthermore, the small number of patients with events precluded any correction for age and infarct site[13] and may account for the conservative results in Table IV.

Clinical implications: The prognostic value of the SA ECG is currently based on studies in which sudden death and ventricular tachycardia have been grouped together as arrhythmic events.[1,2] Our results show that this strategy may be inappropriate. Our results also impact on the interpretation of the SA ECG after thrombolytic therapy. Thrombolysis may result in patchy myocardial damage,[16,17] which may still support rapid ventricular tachycardia, but which does not result in sufficient conduction delay to meet criteria for diagnosing late potentials. The actual values of the electrocardiographic variables may be more reliable for risk stratification in such patients.

That all 3 variables had to be abnormal for the stratification of patients at risk of sudden death, but only 2 abnormal values were needed for predicting ventricular tachycardia, may indicate that the substrate in patients presenting with cardiac arrest may be more specific and difficult to define using the SA ECG than in patients presenting with stable ventricular tachycardia.

Extrapolation of our results to other postinfarct populations depends on the proportion of our sudden deaths that were due to the deterioration of ventricular tachycardia and on whether the electrophysiologic determinants of the risk of developing ventricular fibrillation are the same during acute ischemia as they are during ventricular tachycardia. However, the present approach may be refined by taking age into consideration.[13] Because younger patients have less severe coronary artery disease than older patients, the relative proportion of sudden deaths due to the deterioration of ventricular tachycardia in such patients may be high, and it may thus be easier to differentiate the risk of sudden death and stable ventricular tachycardia in younger than in older patients by using the SA ECG. Further follow-up is needed to examine this hypothesis.

TABLE IV Stratification of Sudden Death and Ventricular Tachycardia Using any Two Signal-Averaged Electrocardiographic Variables*

Sensitivity (%)	SD TP	SD FP	VT TP	VT FP	p Values
40	5	6	6	17	NS
50	6	10	7	19	NS
60	7	16	8	23	NS
70	8	18	10	66	<0.045
Using all Three Signal-Averaged Electrocardiographic Variables					
40	5	5	6	33	<0.033
50	6	11	7	38	<0.091
60	7	16	8	46	<0.104
70	8	19	10	66	<0.054

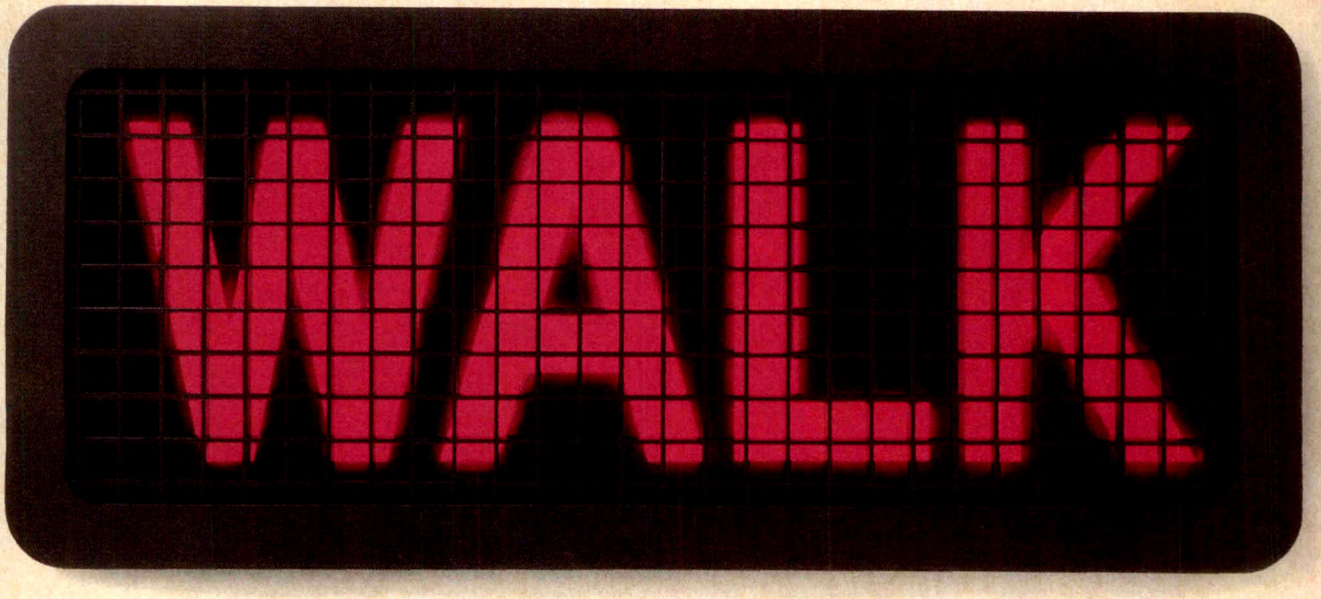
*The number of false-positives and false-negatives for different values of sensitivity. The difference in the positive predictive accuracy between the sudden death and ventricular tachycardia group was examined using Fisher's test ($p < .$).
FP = false-positive patients; NS = not significant; SD = sudden death; TP = true-positive patients; VT = ventricular tachycardia.

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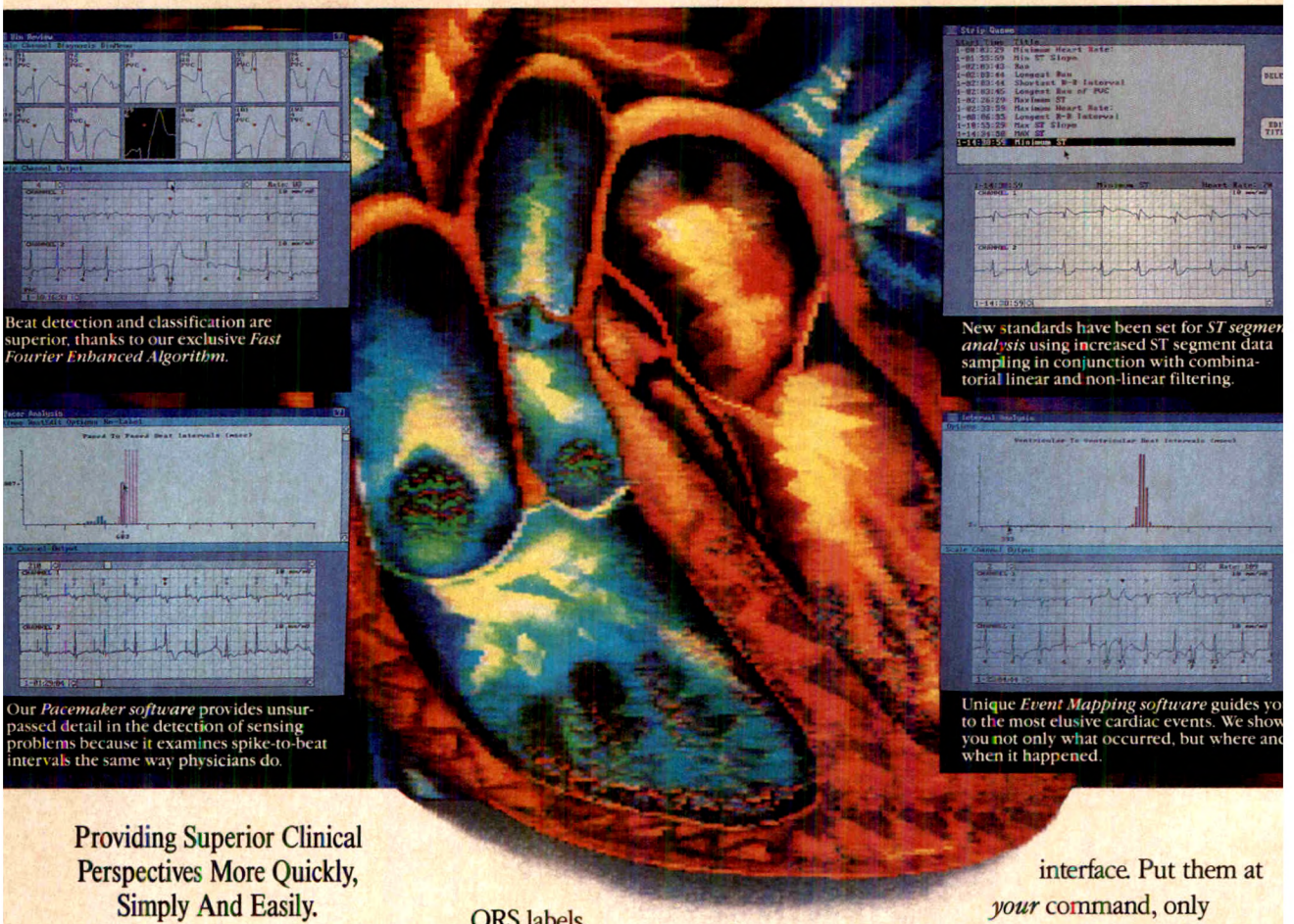
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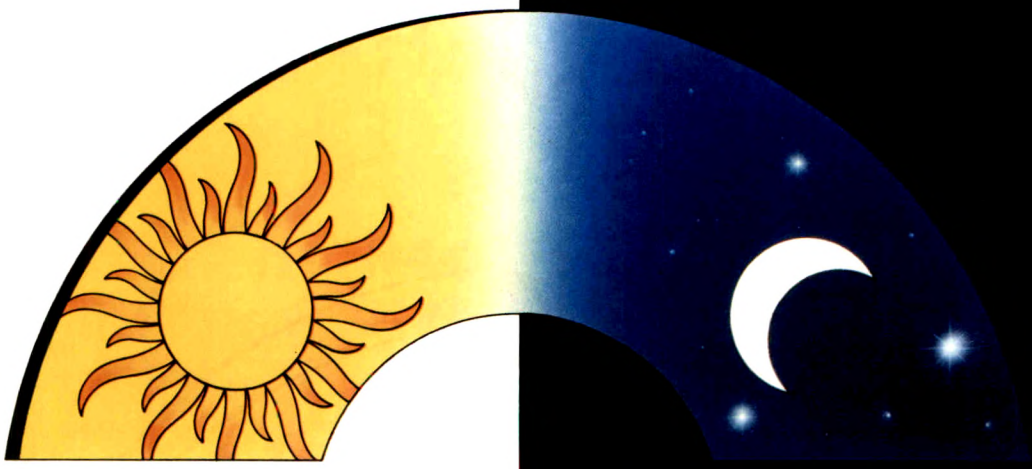
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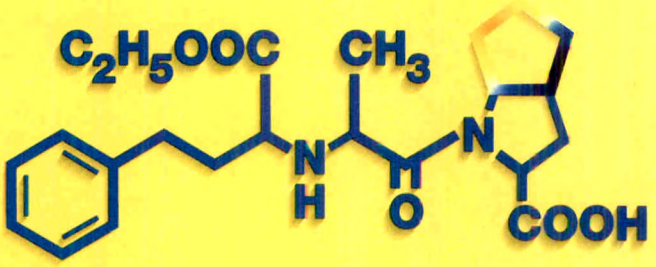
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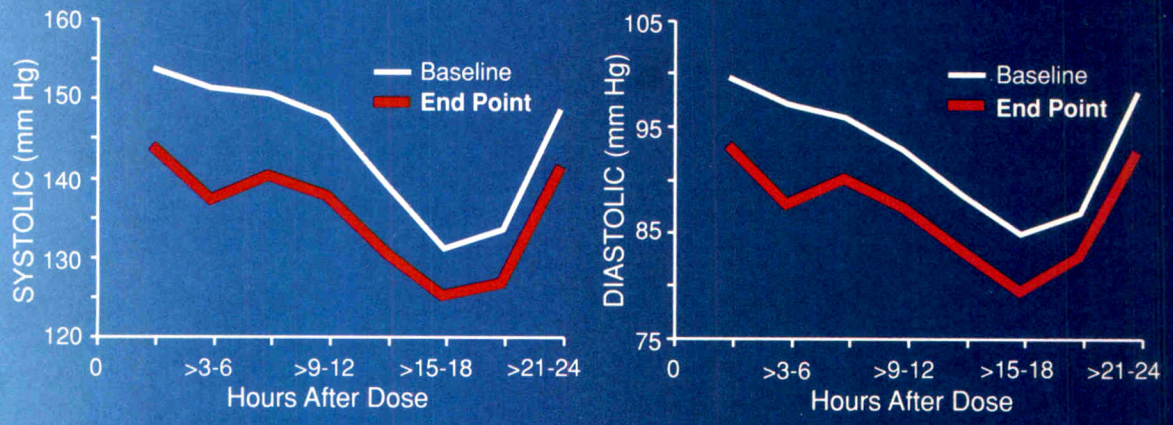
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Available in Easy-to-Swallow Capsules



1.25 mg 2.5 mg 5 mg 10 mg

Usual Starting Dose–2.5 mg Once-a-Day

BRIEF SUMMARY

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, ALTACE should be discontinued as soon as possible **See WARNINGS: Fetal/neonatal morbidity and mortality.**

ALTACE is available in potencies of 1.25 mg, 2.5 mg, 5 mg, and 10 mg in color-coded, hard gelatin capsules.

INDICATIONS AND USAGE: ALTACE is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ALTACE, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that ALTACE does not have a similar risk. (See WARNINGS.)

CONTRAINDICATIONS: ALTACE is contraindicated in patients who are hypersensitive to this product and in patients with history of angioneurotic edema.

WARNINGS: ***Angioedema:*** Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with angiotensin converting enzyme inhibitors. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ALTACE should be discontinued and appropriate therapy instituted immediately. **Where there is involvement of the tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1,000 (0.3 ml to 0.5 ml) should be promptly administered.** (See ADVERSE REACTIONS.)

Hypotension: ALTACE can cause symptomatic hypotension, after either the initial dose or a later dose when the dosage has been increased. Like other ACE inhibitors, ramipril has been only rarely associated with hypotension in uncomplicated hypertensive patients. Symptomatic hypotension is most likely to occur in patients who have been volume- and/or salt-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume and/or salt depletion should be corrected before initiating therapy with ALTACE.

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ALTACE therapy should be started under close medical supervision, they should be followed closely for the first 2 weeks of treatment and whenever the dose of ramipril or diuretic is increased.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with intravenous infusion of physiological saline. ALTACE treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis: Another angiotensin converting enzyme inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in uncomplicated patients, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials of ramipril are insufficient to show that ramipril does not cause agranulocytosis at similar rates. Monitoring of white blood cell counts should be considered in patients with collagen-vascular disease, especially if the disease is associated with impaired renal function.

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. More than 100 cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible and irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ALTACE as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examination should be performed to assess the intra-amniotic environment.

If oligohydramnios is observed, ALTACE should be discontinued unless it is considered lifesaving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be apparent until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function. ALTACE, which crosses the placenta, can be removed from the neonatal circulation by these means, but limited experience has not shown that such removal is central to the treatment of these infants.

No teratogenic effects of ALTACE were seen in studies of pregnant rats, rabbits, and cynomolgus monkeys. On a mg/kg basis, the doses used were up to 2,500 times (in rats), 6.25 times (in rabbits), and 1,250 times (in monkeys) the maximum recommended human dose.

PRECAUTIONS: ***General:*** *Impaired Renal Function.* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe congestive heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin converting enzyme inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine may occur. Experience with another angiotensin converting enzyme inhibitor suggests that these increases are usually reversible upon discontinuation of ALTACE and/or diuretic therapy. In such patients renal function should be monitored during the first few weeks of therapy. Some hypertensive patients with no apparent pre-existing renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when ALTACE has been given concomitantly with a diuretic. This is more likely to occur in patients with pre-existing renal impairment. Dosage reduction of ALTACE and/or discontinuation of the diuretic may be required.

Evaluation of the hypertensive patient should always include assessment of renal function.

Hyperkalemia: In clinical trials, hyperkalemia (serum potassium greater than 5.7 mEq/L) occurred in approximately 1% of hypertensive patients receiving ALTACE. In most cases, these were isolated values, which resolved despite continued therapy. None of these patients was discontinued from the trials because of hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ALTACE. (See DRUG INTERACTIONS.)

Cough: Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough.

Impaired Liver Function: Since ramipril is primarily metabolized by hepatic esterases to its active moiety, ramiprilat, patients with impaired liver function could develop markedly elevated plasma levels of ramipril. No formal pharmacokinetic studies have been carried out in hypertensive patients with impaired liver function.

Surgery/Anesthesia: In patients undergoing surgery or during anesthesia with agents that produce hypotension, ramipril may block angiotensin II formation that would otherwise occur secondary to compensatory renin release. Hypotension that occurs as a result of this mechanism can be corrected by volume expansion.

Information for Patients: *Angioedema:* Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, eyes, lips, tongue, or difficulty in breathing) and to take no more drug until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first days of therapy, and it should be reported. Patients should be told that if syncope occurs, ALTACE™ (ramipril) should be discontinued until the physician has been consulted.

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope.

Hyperkalemia: Patients should be told not to use salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to promptly report any indication of infection (e.g., sore throat, fever), which could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should also be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *With Diuretics:* Patients on diuretics, especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ALTACE. The possibility of hypotensive effects with ALTACE can be minimized by either discontinuing the diuretic or increasing the salt intake prior to initiation of treatment with ALTACE. If this is not possible, the starting dose should be reduced.

With Potassium Supplements and Potassium-Sparing Diuretics: ALTACE can attenuate potassium loss caused by thiazide diuretics. Potassium-sparing diuretics (spironolactone, amiloride, triamterene, and others) or potassium supplements can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution, and the patient's serum potassium should be monitored frequently.

With Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving ACE inhibitors during therapy with lithium. These drugs should be coadministered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, the risk of lithium toxicity may be increased.

Other: Neither ALTACE nor its metabolites have been found to interact with food, digoxin, or antacid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of a tumorigenic effect was found when ramipril was given by gavage to rats (up to 500 mg/kg/day for 24 months) or to mice (up to 1,000 mg/kg/day for 18 months). Dosages greatly in excess of those recommended for humans produced hypertrophy of the renal juxtaglomerular apparatus in mice, rats, dogs, and monkeys. No mutagenic activity was detected in the Ames test in bacteria, the micronucleus test in mice, unscheduled DNA synthesis in a human cell line, or a forward gene-mutation assay in a Chinese hamster ovary cell line. Several metabolites and degradation products of ramipril were also negative in the Ames test. A study in rats with dosages as great as 500 mg/kg/day did not produce adverse effects on fertility.

Pregnancy: **Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS: Fetal/neonatal morbidity and mortality.**

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Geriatric Use: Of the total number of patients who received ramipril in US clinical studies of ALTACE 11.0% were 65 and over while 0.2% were 75 and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

One pharmacokinetic study conducted in hospitalized elderly patients indicated that peak ramiprilat levels and area under the plasma concentration time curve (AUC) for ramiprilat are higher in older patients.

Pediatric Use: Safety and effectiveness in children has not been established.

ADVERSE REACTIONS: ALTACE has been evaluated for safety in over 4,000 patients with hypertension; of these, 1,230 patients were studied in US controlled trials, and 1,107 were studied in foreign controlled trials. Almost 700 of these patients were treated for at least one year. The overall incidence of reported adverse events was similar in ALTACE and placebo patients. The most frequent clinical side effects (possibly or probably related to study drug) reported by patients receiving ALTACE in US placebo-controlled trials were: headache (5.4%), "dizziness" (2.2%) and fatigue or asthenia (2.0%), but only the last was more common in ALTACE patients than in patients given placebo. Generally, the side effects were mild and transient, and there was no relation to total dosage within the range of 1.25 to 20 mg. Discontinuation of therapy because of a side effect was required in approximately 3% of US patients treated with ALTACE. The most common reasons for discontinuation were: cough (1.0%), "dizziness" (0.5%), and impotence (0.4%).

The side effects considered possibly or probably related to study drug that occurred in US placebo-controlled trials in more than 1% of patients treated with ALTACE are shown below.

PATIENTS IN US PLACEBO-CONTROLLED STUDIES

	Altace (N = 651)		Placebo (N = 286)	
	n	%	n	%
Headache	35	5.4	17	5.9
"Dizziness"	14	2.2	9	3.1
Asthenia (Fatigue)	13	2.0	2	0.7
Nausea/Vomiting	7	1.1	3	1.0

In placebo-controlled trials, there was also an excess of upper respiratory infection and flu syndrome in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ramipril patients, with about 4% of these patients requiring discontinuation of treatment. Other adverse experiences reported in controlled clinical trials (in less than 1% of ramipril patients), or rarer events seen in postmarketing experience, include the following. (In some a causal relationship to drug use is uncertain.):

Cardiovascular: Symptomatic hypotension (reported in 0.5% of patients in US trials) (see PRECAUTIONS and WARNINGS), syncope (not reported in US trials), angina pectoris, arrhythmia, chest pain, palpitations, myocardial infarction, and cerebrovascular events.

Renal: Some hypertensive patients with no apparent pre-existing renal disease have developed minor, usually transient, increases in blood urea nitrogen and serum creatinine when taking ALTACE, particularly when ALTACE was given concomitantly with a diuretic. (See WARNINGS.)

Angioneurotic Edema: Angioneurotic edema has been reported in 0.3% of patients in US clinical trials. (See WARNINGS.)

Cough: A tickling, dry, persistent, nonproductive cough has been reported with the use of ACE inhibitors. Approximately 1% of patients treated with ALTACE have required discontinuation because of cough. The cough disappears shortly after discontinuation of treatment. (See PRECAUTIONS.)

Gastrointestinal: Abdominal pain (sometimes with enzyme changes suggesting pancreatitis), anorexia, constipation, diarrhea, dry mouth, dyspepsia, dysphagia, gastroenteritis, nausea, increased salivation, taste disturbance, and vomiting.

Dermatologic: Apparent hypersensitivity reactions (manifested by dermatitis, pruritus, or rash, with or without fever), photosensitivity, and purpura.

Neurologic and Psychiatric: Anxiety, amnesia, convulsions, depression, hearing loss, insomnia, nervousness, neuralgia, neuropathy, paresthesia, somnolence, tinnitus, tremor, vertigo, and vision disturbances.

Fetal/Neonatal Morbidity and Mortality: See WARNINGS: Fetal/neonatal morbidity and mortality.

Other: arthralgia, arthritis, dyspnea, edema, epistaxis, impotence, increased sweating, malaise, myalgia, and weight gain.

Clinical Laboratory Test Findings: *Creatinine and Blood Urea Nitrogen:* Increases in creatinine levels occurred in 1.2% of patients receiving ALTACE alone, and in 1.5% of patients receiving ALTACE and a diuretic. Increases in blood urea nitrogen levels occurred in 0.5% of patients receiving ALTACE alone and in 3% of patients receiving ALTACE with a diuretic. None of these increases required discontinuation of treatment. Increases in these laboratory values are more likely to occur in patients with renal insufficiency or those pretreated with a diuretic and, based on experience with other ACE inhibitors, would be expected to be especially likely in patients with renal artery stenosis. (See PRECAUTIONS and WARNINGS.)

Since ramipril decreases aldosterone secretion, elevation of serum potassium can occur. Potassium supplements and potassium-sparing diuretics should be given with caution, and the patient's serum potassium should be monitored frequently. (See PRECAUTIONS and WARNINGS.)

Hemoglobin and Hematocrit: Decreases in hemoglobin or hematocrit (a low value and a decrease of 5 g/dl or 5% respectively) were rare, occurring in 0.4% of patients receiving ALTACE alone and in 1.5% of patients receiving ALTACE plus a diuretic. No US patients discontinued treatment because of decreases in hemoglobin or hematocrit.

Other (causal relationships unknown): Clinically important changes in standard laboratory tests were rarely associated with ALTACE administration. Elevations of liver enzymes, serum bilirubin, uric acid, and blood glucose have been reported, as have scattered incidents of leukopenia, eosinophilia, and proteinuria. In US trials, less than 0.2% of patients discontinued treatment for laboratory abnormalities; all of these were cases of proteinuria or abnormal liver-function tests.

OVERDOSAGE: Human overdoses of ramipril have not been reported, but the most common manifestation of human ramipril overdosage is likely to be hypotension. Because the hypotensive effect of ramipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat ramipril overdose by infusion of normal saline solution.

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Variations in Expression and Treatment of Transient Neurocardiogenic Instability

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Whereas previous reports describe the head-up tilt test for the diagnosis of neurocardiogenic syncope, this study focuses on the events leading up to syncope. These events are part of a spectrum of neurocardiogenic instability; syncope is the extreme end point. This report is based on tilt studies of 108 patients, aged 4 to 22 years (mean 13), with histories of either unexplained syncope or episodes of visual blackout without loss of consciousness. The tilt study was positive in 74% of the patients. Five stages of neurocardiogenic instability were identified, ranging from excessive fluctuations in heart rate to full syncope. Uncommon reactions during the tilt study include dissociation of hypotension, bradycardia and vagal symptoms and extended asystole (>6 seconds). Therapy with β_1-selective blockers was highly successful in suppressing symptoms of neurocardiogenic instability. Repeat tilt testing with β blockade has resulted in either normal or markedly improved stability in heart rate and blood pressure. Neurocardiogenic instability is a common condition occurring between age 10 and 20 years. It appears to be self-limited.

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Since 1989, numerous articles[1–9] have promoted the tilt test for evaluation of neurocardiogenic syncope. All of these reports focus on syncope. There is scant information as to what precedes syncope. This paper describes events that lead up to syncope and which are part of a spectrum of neurocardiogenic instability. Syncope is merely an extreme expression of this spectrum of symptoms.

METHODS

Patients: During the past 3 years, we have studied 108 children (67 girls and 41 boys, aged 4 to 22 years [mean age 13]). Of these, 104 had histories suggestive of neurocardiogenic instability. Recurrent syncope with episodes of presyncope in between was the most common reason for referral (86 patients, including 15 with exercise-related syncope). Eighteen children were seen because of visual blackout episodes or lightheadedness without syncope; 12 had a family history of syncope. Four children had histories not suggestive of neurocardiogenic instability (neurologic or psychiatric disorders in 3, hypoglycemia in 1 patient).

All patients were evaluated by a pediatric cardiologist and were free of heart disease. Three patients had a history of arrhythmia (1 child with atrial tachycardia and 2 with ectopic ventricular beats). Many of the children had electrocardiograms or echocardiograms; one third had neurologic evaluations. These studies were all normal. No patient was taking medication during the tilt evaluation.

All patients were studied in the postabsorptive state. Our tilt protocol has been reported.[7] A 3-lead electrocardiogram (I,II,V_1) was recorded continuously; cuff blood pressures were recorded every 2 minutes. The study was terminated when presyncope or syncope was observed or when a steady heart rate of 150 to 170 beats/min was reached during isoproterenol infusion.

Presyncope is defined as a decrease in heart rate or blood pressure, or both, associated with vagal symptoms such as sweating, nausea and paleness. Presyncope did not necessarily progress to full syncope (loss of consciousness).

RESULTS

Analysis of test responses revealed 5 stages of neurocardiogenic instability; these stages blend into each other without sharp borders. During stage 1, the child displays an excessive degree of fluctuations in heart rate (>20 beats/min); these cyclic changes are variable in frequency, begin with an increase in heart rate, with return to baseline rate within 10 to 20 seconds. During stage 2, sighing and yawning is added to this instability

in heart rate. The child feels "funny"; mild headache is often stated. During stage 3, presyncope gets more apparent; typical symptoms are hyperventilation, sensation of "can't breathe," sweating, feeling hot or cold, nausea, and the child is pale. Not all of these symptoms are seen in a given child. Stage 4 is complete presyncope with a decrease in blood pressure and heart rate, at times associated with loss of vision; muscle tone is still maintained. Stage 5 is full syncope with loss of consciousness, with profound bradycardia or asystole for several seconds. This sequence of symptoms may occur within 10 to 15 seconds or may build up over 1 to 2 minutes. Some children experience only stages 1 and 2 (borderline tilt result), others proceed to stages 3, 4 or 5. Some children restabilize despite continued tilt. The bradycardia of stage 4 is frequently junctional; in one third of the patients sinus bradycardia is observed.

Uncommon events are (1) pronounced vagal symptoms without a marked decrease in heart rate or blood pressure (1 child) — however, some decrease in heart rate to levels of 80 to 110 beats/min is always seen; (2) the decrease in heart rate and blood pressure during stage 4 are not necessarily linked — heart rate may decrease with little change in blood pressure and vice versa (2 children each); (3) seizure activity during syncope (3 children), probably a function of the length of asystole; and (4) asystole lasting between 3 to 10 seconds (5 children).

The recovery after return to the supine position is likewise variable: Full recovery may be very fast, within 1 to 2 minutes, or may take 5 to 10 minutes with continued nodal bradycardia. Most patients feel drained and washed-out after a positive tilt study.

104 children of this group of 108 consecutive tilt studies were diagnosed to have neurocardiogenic syncope. Of these 104 patients, 13 tested normal, 14 had borderline test results (7 each stage 1 and stage 2) and 77 patients had positive tilt study responses (stage 3, 15 patients; stage 4, 47; stage 5, 15). Thus 74% of these patients had positive tilt study responses, i.e., they progressed to stages 3 to 5. Thirteen percent of the children were borderline, i.e., their symptoms remained at stage 1 or 2. In 40%, the positive responses could be induced by simple tilt, and in 60% isoproterenol was added to the upright tilt. All children had normal systolic blood pressure (108 ± 10 mm Hg) and normal resting heart rates (70 ± 12 beats/min).

Depending on the severity of the history and the anxiety level of the family, patients were given medication (68%, 56 girls and 15 boys). We began therapy with a β_1-selective blocker, atenolol, at a low dose (25 or 50 mg/day). Depending on the child's response this dose may have to be increased to 50 mg twice daily. Occasionally, metoprolol or nadolol may be more effective than atenolol. All patients improved with therapy; with 3 exceptions syncope did not recur. Only 3 patients had adverse effects (lethargy, gastrointestinal symptoms, headaches). Fifteen patients discontinued therapy after 6 to 18 months: only 1 of these had a relapse of syncope.

Repeat tilt studies with β blockade were performed in 15 patients whose initial study results were strongly positive. Of these, 10 had completely normal tilt study responses, and 5 significantly improved; syncope was induced in only 2 patients with maximal challenge with isoproterenol. None of these patients had experienced syncope with optimal therapy, and a few had occasional episodes of transient dizziness.

DISCUSSION

A normal response to upright posture is a moderate increase in heart rate and blood pressure, mediated by a widespread activation of the sympathetic nervous system. Additional sympathetic stimulation by means of isoproterenol causes a significant additional increase in heart rate and, to a lesser extent, blood pressure. However, there is neither marked bradycardia nor hypotension[10]; sympathetic and parasympathetic impulses are regulated within a narrow band. This tight regulation is imperfect in neurocardiogenic instability. Neurocardiogenic instability is an exaggeration of normal neurocardiogenic reflexes, an exaggeration of the normal sympathetic surges in heart rate and the vagal counter regulation. When the parasympathetic system overregulates, symptoms of neurocardiogenic instability appear. The decrease in left ventricular stroke volume (and its increase in left ventricular wall stress), thought by some to be the trigger for syncope,[11-15] may be only a by-product of hypotension/bradycardia. Bradycardia and hypotension are not necessarily linked phenomena: Although they occur simultaneously in the typical case, each one may occur, more or less, by itself.

All normal children have fluctuations in heart rate superimposed on sinus arrhythmia; these fluctuations are <20 beats/min. Such fluctuations are not prominent in the supine position but become evident when the child is stressed by simple head-up tilt, without or with isoproterenol challenge. The smaller these fluctuations are, the more stable is the child's circulatory control. In patients with neurocardiogenic instability these fluctuations in heart rate are more pronounced, especially during isoproterenol infusion, and exceed 20 or even 30 beats/min. Neurocardiogenic instability is probably a common condition during teenage years. It occurs more frequently in girls than in boys (girls/boys, 1.6). Its symptomatic expression is highly variable among patients and within the same patient from day to day. We were not able to detect a "typical" personality pattern that may indicate a propensity for neurocardiogenic instability. Although some of our children were excessively apprehensive, most children took a very rational, common-sense approach to this test. There is frequently a family history of neurocardiogenic instability.

In contrast to the common association of syncope and arrhythmia in adult patients,[9,15-18] we have seen only 1 child with neurocardiogenic instability and a significant rhythm disturbance (undocumented supraventricular tachycardia). Therapy with low-dose β blockade has been very useful in suppressing symptoms of neurocardiogenic instability. We have preferred β_1-cardioselective blockers; other investigators have used clonidine,[16] disopyramide,[16] scopolamine[5] and fluorinated mineralocorticoids.[4,5] Any evaluation of drug efficacy has to take the spontaneous fluctuations in neurocardio-

genic instability into account. The duration of therapy cannot be predicted for a given child.

Because most parents who seek pediatric advice for syncope are informed and concerned parents, it is important to explain the nature and transient character of this problem. We provide an information sheet for parent and child that has proved not only helpful, but also time-saving for all involved parties.

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Racial Differences in Left Ventricular Structure in Healthy Young Adults

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Racial differences in cardiac structure and function were evaluated in 62 black and 71 white healthy young adults. Left ventricular (LV) mass index, relative wall thickness, fractional shortening, resting cardiac index and resting systemic vascular resistance index were estimated using M-mode echocardiography. Pulsed Doppler interrogation of transmitral flow was used to characterize LV filling. Average daytime blood pressure (BP) was determined by ambulatory monitoring during a typical work or school day. Ambulatory daytime BP averaged 127 ± 12/80 ± 7 mm Hg in black subjects, and 127 ± 9/80 ± 6 mm Hg in white subjects (p = not significant). The 2 groups were also similar in resting BP, age and gender composition. Relative wall thickness was significantly greater in black than in white subjects (0.37 ± 0.06 vs 0.34 ± 0.05; p <0.01). This difference was found in both men and women. Black subjects also had a higher resting systemic vascular resistance index (2,110 ± 570 vs 1,920 ± 500 dynes · s · cm^{-5} · m^2; p <0.05) and lower resting cardiac index (3.14 ± 0.84 vs 3.46 ± 0.85 L/min/m^2; p <0.05). There were no significant differences between black and white subjects in LV mass index, fractional shortening and normalized peak filling velocity. These results suggest that racial differences in LV structure and systemic hemodynamics exist even in patients without sustained hypertension. In our study population, the greater relative wall thickness in black subjects was not accompanied by significant differences in LV systolic function or diastolic filling.

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Epidemiologic studies have demonstrated a greater prevalence of hypertensive heart disease in black subjects than in their white counterparts. In the Evans County study[1] and the Hypertension Detection and Follow-Up Program,[2] electrocardiographic evidence of left ventricular (LV) hypertrophy was 2 to 4 times as likely in black as in white subjects with comparable levels of blood pressure (BP). Several subsequent studies using echocardiography to more precisely evaluate cardiac structure confirmed a greater propensity for black hypertensive patients to develop LV hypertrophy.[3,4] It is not clear whether these findings reflect racial differences present at all levels of BP or represent differences in cardiac adaptation to established essential hypertension. To further evaluate racial differences in LV structure, we studied a group of healthy young adults with normal or marginally elevated BP.

METHODS

Subjects: The protocol was approved by the institutional committee on the protection of the rights of human subjects, and written, informed consent was obtained from all subjects before participation. The study population of 133 volunteers was selected from 160 adults between the ages of 18 and 47 years. No subject had a history of sustained hypertension or other chronic illness, or had received antihypertensive medications. There were 29 black men, 33 black women, 36 white men and 35 white women in the study. All subjects were either employed full-time outside the home (n = 92) or were full-time students (n = 41).

Of the 160 subjects who agreed to participate in the study, 27 were omitted from this analysis because of technically inadequate M-mode echocardiograms or Doppler studies of LV inflow, inability to complete the ambulatory BP monitoring session, or high BP noted on screening examination (diastolic BP >95 mm Hg, or systolic BP >160 mm Hg).

The height and weight of each subject were measured at the time of recruitment. Body surface area was calculated by the formula of Dubois,[5] and body mass index as weight/height.[2]

Echocardiographic and Doppler measurements: Echocardiograms and Doppler studies were performed with a Hewlett-Packard 77020 ultrasound imaging system equipped with a 2.5 MHz phased-array scanner. M-mode images of the left ventricle were obtained from the parasternal windows with the patient in the left lateral decubitus position. Pulsed-wave Doppler measurements of diastolic transmitral flow were recorded just below the mitral annulus from the apical window. Tracings were recorded on strip chart paper at 100 mm/s.

All studies were interpreted blindly by an experienced echocardiographer. The end-diastolic thicknesses

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of the LV posterior wall and interventricular septum, and the dimensions of the left ventricle in end-diastole and end-systole were measured on ≥3 cardiac cycles according to the recommendations of the American Society of Echocardiography.[6] LV mass was estimated using a corrected cube function model as described by Devereux et al[7] and divided by body surface area to yield LV mass index. Relative wall thickness was defined as twice the ratio of posterior wall thickness to LV end-diastolic dimension. Fractional shortening (an index of LV systolic performance) was calculated as the difference between LV end-diastolic and end-systolic dimensions divided by LV end-diastolic dimension. Cardiac index was determined using measurements of stroke volume derived from cube function estimates of end-diastolic and end-systolic LV volumes.[8] Systemic vascular resistance index was estimated by standard formulas using simultaneous cardiac index and BP measurements.[9] LV filling was assessed using pulsed-wave Doppler to measure the peak velocity of diastolic filling normalized to mitral stroke volume, as previously described by Bowman et al.[10] This index was calculated as the ratio of peak early diastolic flow velocity to the time-velocity integral of mitral inflow.

Resting blood pressure measurements: Casual BP was determined during the screening examination by averaging ≥4 measurements obtained with the subject in the seated position, using the first and fifth phases of Korotkoff's sounds. Resting supine BP was measured during echocardiography with an Accutorr monitor. Initially, ≥3 simultaneous readings were obtained with the usual auscultatory technique to provide standardization. Measurements were then automatically obtained every 2.5 minutes as the ultrasound study was performed. BP readings during M-mode imaging of the left ventricle (generally performed after approximately 20 minutes of supine rest) were used to calculate systemic vascular resistance index.

Ambulatory blood pressure measurements: Ambulatory BP measurements were obtained with the Accutracker 103 monitor. Subjects were instrumented for ambulatory monitoring between 7 and 10 A.M. of a typical work or school day. A minimum of 3 sitting and 3 standing readings were obtained concurrently with the Accutracker and by auscultation to provide standardization with the usual clinical technique. Readings were then obtained 4 times an hour at unpredictable intervals (7 to 23 minutes apart). The device was removed by the patient at bedtime and returned to the laboratory on the following day.

BP records were inspected by an experienced observer to exclude artifactual readings, as recommended by Harshfield et al.[11] Mean ambulatory systolic and diastolic BPs were determined by averaging all acceptable measurements during the monitoring period.

Assessment of physical activity: Routine exercise patterns were assessed by questionnaire and converted into a numerical estimate of the weekly energy expenditure that was due to physical activity, as described previously.[12] Each subject was assigned a physical activity score of 0 (no reported regular aerobic activity), 1 (infrequent exercise) or 2 (regular exercise of sufficient frequency and intensity to result in cardiovascular conditioning).

TABLE I Clinical Features of the Study Population by Race

	Black	White	p Value
Mean age (yr)	30 ± 7	31 ± 6	NS
Men/women	47%/53%	51%/49%	NS
Body surface area (m^2)	1.90 ± 0.21	1.84 ± 0.20	NS
Body mass index (kg/m^2)	26.1 ± 4.4	23.8 ± 3.6	<0.01
Physical activity score	0.7 ± 0.8	1.2 ± 0.8	<0.01
Casual systolic blood pressure (mm Hg)	118 ± 13	120 ± 13	NS
Casual diastolic blood pressure (mm Hg)	74 ± 10	75 ± 9	NS
Daytime systolic blood pressure (mm Hg)	127 ± 12	127 ± 9	NS
Daytime diastolic blood pressure (mm Hg)	80 ± 7	80 ± 6	NS

All values expressed as mean ± SD.
NS = not significant.

Analysis of data: Mean values and standard deviations for each analyzed variable were calculated for black and white subjects, and for men and women within each racial group. The significance of differences between groups was tested by analysis of variance. Multiple linear regression techniques were used to assess the relation of LV relative wall thickness to race after adjustment for related variables (i.e., body mass index and level of routine physical activity).

RESULTS

Clinical features: The mean age for the study population was 30 ± 7 years. Casual systolic and diastolic BPs averaged 119 ± 13 mm Hg (range 92 to 152) and 75 ± 9 mm Hg (range 52 to 95), respectively; ambulatory daytime systolic and diastolic BPs averaged 127 ± 10 mm Hg (range 108 to 159) and 80 ± 7 mm Hg (range 65 to 99), respectively. Clinical features of subjects in the 2 racial groups are listed in Table I. Black and white subjects were similar in age and gender. Black subjects were slightly more obese, as reflected by a greater body mass index, and were less likely to engage in regular physical activity. Mean casual and ambulatory systolic and diastolic BPs were nearly identical in the 2 groups.

Echocardiographic assessment of left ventricular structure and function: Significant racial differences in LV geometry were observed (Table II). Black subjects had a smaller LV end-diastolic dimension, and tended to have greater posterior wall and interventricular septal thicknesses than those of their white counterparts. As a result, black subjects had a significantly greater mean relative wall thickness, but there was no significant difference between the groups in estimated LV mass index. Indexes of LV contraction (fractional shortening) and diastolic filling (normalized peak filling velocity) were similar in the 2 groups.

Hemodynamics: Although resting BP was similar in black and white subjects, there was a significant racial difference in the hemodynamic profile (Table III). Black subjects tended to have a lower cardiac index and

TABLE II Echocardiographic and Doppler Measurements by Race

	Black	White	p Value
Left ventricular mass index (g/m^2)	84 ± 18	86 ± 16	NS
Left ventricular relative wall thickness	0.37 ± 0.06	0.34 ± 0.05	<0.01
Left ventricular end-diastolic dimension (mm)	49 ± 5	51 ± 5	<0.05
Posterior wall thickness (mm)	9.1 ± 1.4	8.7 ± 1.2	NS
Interventricular septal thickness (mm)	9.3 ± 1.4	8.6 ± 1.4	<0.05
Left ventricular fractional shortening	0.37 ± 0.07	0.36 ± 0.05	NS
Left ventricular normalized peak filling velocity	7.8 ± 1.2	7.9 ± 1.3	NS

All values expressed as mean ± SD.
NS = not significant.

TABLE III Resting Hemodynamics by Race

	Black	White	p Value
Resting supine systolic blood pressure (mm Hg)	114 ± 14	116 ± 12	NS
Resting supine diastolic blood pressure (mm Hg)	67 ± 9	67 ± 10	NS
Cardiac index (L/min/m^2)	3.14 ± 0.84	3.46 ± 0.85	<0.05
Systemic vascular resistance index (dynes · s · cm^{-5} · m^2)	2,110 ± 570	1,920 ± 500	<0.05

All values expressed as mean ± SD.
NS = not significant.

higher systemic vascular resistance index than did whites.

Further analyses: Racial differences in LV relative wall thickness were significant in both men and women (Table IV). Although the tendency of black subjects to have a higher systemic resistance index and lower cardiac index was observed in both genders, these differences did not uniformly achieve statistical significance. Greater LV relative wall thickness in black subjects was also noted in both students and employed subjects.

After adjustment for body mass index and activity score by multiple regression techniques, relative wall thickness continued to show a significant relation to race ($p < 0.01$ after adjusting for body mass index; $p < 0.05$ after adjusting for activity score). Thus, the effects of race on LV structure were at least in part independent of associated differences in body size and level of routine physical activity.

DISCUSSION

LV hypertrophy is an independent risk factor for cardiovascular morbidity and mortality.[13–15] Although ventricular afterload is an important determinant of structural characteristics of the left ventricle, the correlations between BP and LV mass or relative wall thickness are relatively weak. Whether expressed as casual office determinations[16–18] or parameters derived from ambulatory monitoring such as work pressure,[16] pressure "load"[17] or nighttime pressure,[18] BP accounts for less than half of the variance in LV mass. This may in part be explained by the potential influence of such factors as demographic characteristics[12,19] and neurohumoral substances[20,21] on LV dimensions.

Our study demonstrates that race is an important determinant of LV structure in healthy young subjects without established hypertension. In a cohort of black and white subjects who were closely matched for age, gender and BP, blacks had a significantly greater ratio of wall thickness to chamber dimension. This difference (found in both men and women) was independent of body mass index and reported physical activity. LV systolic performance (as assessed by fractional shortening) and diastolic filling (determined by Doppler measurement of transmitral flow) were similar in black and white subjects. Although levels of resting BP were nearly identical, black subjects had a higher mean systemic vascular resistance index.

Racial differences in LV structure in patients with established hypertension were described by previous investigators. Dunn et al,[3] in a comparison of black and white hypertensive patients matched for gender and BP, found a significantly greater average LV mass index in blacks. Hammond et al[4] evaluated 75 hypertensive patients from a middle-aged working population in New York City and observed racial differences similar to those described in our study. Black and white hyperten-

TABLE IV Clinical Features, Echocardiographic Measurements and Resting Hemodynamics by Race in Men and Women

	Men			Women		
Variables	Black (n = 29)	White (n = 36)	p Value	Black (n = 33)	White (n = 35)	p Value
Age (yr)	31 ± 9	31 ± 7	NS	30 ± 6	30 ± 6	NS
Body mass index (kg/m^2)	26.3 ± 3.9	24.2 ± 2.4	<0.05	25.9 ± 4.9	23.4 ± 4.6	<0.05
Daytime systolic blood pressure (mm Hg)	133 ± 11	129 ± 7	NS	122 ± 10	124 ± 10	NS
Daytime diastolic blood pressure (mm Hg)	84 ± 6	82 ± 5	NS	77 ± 6	79 ± 7	NS
Left ventricular mass index (g/m^2)	96 ± 17	92 ± 14	NS	73 ± 12	79 ± 16	NS
Left ventricular relative wall thickness	0.38 ± 0.06	0.34 ± 0.06	<0.05	0.37 ± 0.06	0.34 ± 0.04	0.05
Left ventricular fractional shortening	0.36 ± 0.08	0.36 ± 0.06	NS	0.37 ± 0.06	0.36 ± 0.04	NS
Left ventricular normalized peak filling velocity	7.4 ± 1.2	7.8 ± 1.2	NS	8.0 ± 1.1	7.9 ± 1.5	NS
Cardiac index (L/min/m^2)	3.34 ± 0.88	3.58 ± 0.77	NS	2.97 ± 0.76	3.32 ± 0.91	NS
Systemic vascular resistance index (dynes · s · cm^{-5} · m^2)	2,080 ± 590	1,810 ± 400	<0.05	2,140 ± 570	2,020 ± 580	NS

All values are expressed as mean ± SD.
NS = not significant.

sive patients were similar in age, BP and LV mass; however, blacks had a significantly greater mean relative wall thickness. A similar trend was noted in normotensive subjects from the same population, although the differences did not achieve statistical significance.

Our data suggest that the greater propensity of hypertensive black patients to develop concentric LV hypertrophy does not represent simply a difference in the cardiac adaptation to high levels of BP, but reflects a difference between the races that can be observed even in young, normotensive subjects. The etiology of this racial difference in LV geometry is uncertain. Our finding that black and white subjects have different hemodynamic profiles is consistent with several previous reports[4,22] and suggests that differences in cardiac structure may be a consequence of vascular properties that result in a higher peripheral resistance in blacks. Alternatively, racial differences in diurnal BP variation or BP responses to stress may be important determinants of LV structure. Harshfield et al[23] found a greater nocturnal decrease in BP in white adolescent boys than in age-matched black subjects, a phenomenon that may protect against the development of LV hypertrophy.[18] A number of investigators noted an exaggerated cardiovascular reactivity in black subjects in response to either behavioral[24-26] or physical[27,28] stressors. Although the pathophysiologic significance of this greater BP reactivity in normotensive black subjects is uncertain, animal studies suggest that repeated pressor episodes may stimulate adaptive structural changes in the left ventricle, even in the absence of sustained hypertension.[29]

Although a clear racial difference in LV structure was noted in our subjects, no associated differences in ventricular function were apparent. Both fractional shortening (an ejection phase index of systolic function) and normalized peak filling velocity (a Doppler index of diastolic filling) were similar in black and white subjects. However, the pattern of increased relative wall thickness noted in black subjects may be deleterious. In a large cohort of hypertensive subjects followed by Koren et al,[30] those with an increased relative wall thickness had a high risk of cardiovascular events, even if the calculated LV mass was normal. Thus, structural characteristics of the left ventricle may contribute to the greater morbidity and mortality from cardiovascular disease observed in the black population.

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Comparison of the Effects of Isradipine and Lisinopril on Left Ventricular Structure and Function in Essential Hypertension

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The effects on cardiac structure and function of antihypertensive regimens with different effects on the renin-angiotensin system were compared. In a 1-year study, 32 patients with essential hypertension were randomized to treatment with either the converting enzyme inhibitor lisinopril or the calcium antagonist isradipine; hydrochlorothiazide could be added. Blood pressure (BP) decreased significantly ($p < 0.001$) and similarly in the 2 treatment groups. Left ventricular (LV) mass was already significantly reduced after 16 weeks of treatment ($p < 0.001$) and remained decreased thereafter, with no difference in the response to the 2 treatment regimens. The change in LV mass was related to the decrease in systolic BP for the total study group ($p < 0.001$) and for each treatment group separately. During the 3-week run-out period on placebo, BP and LV mass increased again ($p < 0.01$). Afterload decreased during active treatment ($p < 0.001$), and fractional shortening of the LV internal diameter was significantly increased ($p < 0.01$) to a similar extent in both groups. The ratio of peak mitral flow velocities during atrial contraction and early filling was reduced after 1 year of active treatment in the total study group ($p < 0.01$); this change was similar in both groups.

The data suggest that the regression of LV mass during antihypertensive therapy is mainly related to the decrease in systolic BP.

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Hypertension can lead to the development of left ventricular (LV) hypertrophy.[1] LV systolic function is usually normal,[1,2] whereas abnormalities in diastolic function appear to occur early in hypertension.[1–4] LV hypertrophy is associated with an increased incidence of cardiovascular complications, independent of the increase in blood pressure (BP).[5] Therefore, reversion of these cardiac structural changes may improve diastolic function and the prognosis of the hypertensive patient. Furthermore, based on in vitro tissue culture studies, angiotensin II was proposed as a trophic factor in the development of LV hypertrophy in hypertensive patients.[6] To elucidate the importance of the renin-angiotensin system in LV hypertrophy in essential hypertension, comparison of the regression of LV mass by a drug that suppresses angiotensin II generation and by a drug that has little influence on the angiotensin II level may be useful. Therefore, we performed a 1-year follow-up study in which hypertensive patients were randomized to treatment with either the converting enzyme inhibitor lisinopril or the calcium antagonist isradipine. Cardiac structure, and systolic and diastolic functions were investigated by use of imaging echocardiography and Doppler velocimetry in the LV inflow and outflow tracts.

METHODS

Patients: Patients with essential hypertension, aged ≥18 years, and in World Health Organization stages I and II were eligible for the study. Patients with any disease that could interfere with the study protocol were excluded, as well as women when pregnant, lactating, seeking pregnancy or receiving oral contraceptives.

Treatment protocol: Patients with a good quality echocardiogram entered a 4-week run-in period during which they received 1 placebo tablet each morning. They were examined after 2 and 4 weeks, but this period could be shortened when hypertension was severe. Patients who met the BP criteria on the final day of placebo treatment (supine diastolic BP >95 mm Hg or systolic BP >145 mm Hg, or both) were randomized to the isradipine or lisinopril treatment group after stratification for diastolic BP (<95 and ≥95 mm Hg) and LV mass (<3 and ≥3 g/kg of body weight). Subsequent visits were scheduled after 4, 8, 16, 24, 38 and 52 weeks. Active treatment was followed by a placebo run-out period of 3 weeks. Treatment with lisinopril began with 10 mg once daily; the initial dose of isradipine was 2 × 1.25 mg/day in 10 patients, which was increased to 2 × 2.5 mg/day (n = 6) during the course of the study. The

dose of each drug could be doubled at each visit to a maximum of 40 mg/day of lisinopril or 2 × 5 mg/day of isradipine, if diastolic BP was >90 mm Hg or if systolic BP was >140 mm Hg. At week 16, hydrochlorothiazide (25 mg/day) could be added if diastolic BP was >100 mm Hg. BP measurements and echocardiography were performed by 1 blinded observer. Adjustments of drug treatment were based on BP measured by the observer, taking side-effects into account.

Of the randomized patients, half had not been treated with antihypertensive drugs. Previous medication had been stopped for an average of 10.1 weeks in 9 isradipine-treated patients and for 11.6 weeks in 7 lisinopril-treated patients.

Methods: All measurements were performed in the morning after the patients received their last medication at home. A clinical examination (including measurement of body height) was performed initially; at each visit, body weight was measured, and a standard 12-lead electrocardiogram was obtained. After 10 minutes of recumbency in a quiet room, systolic and diastolic BP, and heart rate were measured 5 times by use of an automatic device (Dinamap® 845, Applied Medical Research Corporation, Tampa, Florida 33607), with 2-minute intervals between the measurements. Recumbent BP was then measured 5 times by 1 investigator using a mercury sphygmomanometer (Korotkoff phase V for diastolic BP). Pulse rate was measured by palpation of the radial pulse for 30 seconds. The patient then assumed the standing position for 1 minute, after which BP was measured 3 times and pulse rate for 30 seconds.

ECHOCARDIOGRAPHY: M-mode echocardiography with bidimensional guidance was performed using a 3.5 MHz transducer and an Ultra-Imager (Honeywell Inc., Denver, Colorado) with photographic registration at a paper speed of 100 mm/s. Measurements were performed at end-expiration. LV inflow Doppler echocardiography was performed with a 3.5 MHz transducer, visualizing the apical 4-chamber view. Aortic Doppler flow measurements were obtained from the suprasternal notch, using a 2.25 MHz transducer with a special design for easy access to the suprasternal notch. The details were previously reported.[7]

ANALYSIS OF ECHOCARDIOGRAPHIC DATA: The echocardiographic tracings of each subject were randomized and coded. After agreement on the reading of the tracings by 2 blinded observers, they were processed by 1 observer using a Houston Instrument HIPAD digitizer tablet connected to a personal computer. On each tracing, 3 to 5 heart beats were analyzed, and values were averaged. Measurements on the echocardiograms (i.e., LV wall thickness and internal diameter) were performed according to the recommendations of the American Society of Echocardiography.[8] LV total diameter, mean and relative wall thicknesses, LV mass, fractional shortening and end-systolic LV meridional wall stress were calculated; the details of the analysis were previously described.[9] LV peak inflow velocity in the early (E) rapid filling and late (A) atrial contraction phases, and the surface area under the Doppler curves were measured. The ratios of late/early diastolic peak flow velocity and late/early surface area were calculated. Peak aortic flow velocity and the area under the flow velocity curve or stroke distance were measured. Minute distance was calculated as stroke distance times heart rate. Linear resistance was calculated as mean BP/minute distance, representing the Doppler index of systemic vascular resistance[10]; mean BP was calculated as: [(systolic − diastolic BP)/3] + diastolic BP.

Biochemical measurements: Plasma angiotensin-converting enzyme activity was measured spectrophotometrically, as previously described.[11] Plasma renin activity was measured by radioimmunoassay, according to the method of Fyhrquist and Puutula.[12] Plasma norepinephrine was determined by high-performance liquid chromatography with electrochemical detection.[13] Urinary sodium concentration was measured with 24-hour urine collections by use of a Technicon SMA12 apparatus; 24-hour urinary sodium excretions were calculated.

Statistical analysis: Data are reported as arithmetic mean ± SD or SE. The distributions of plasma renin activity and plasma norepinephrine were positively skewed. To normalize the distribution, plasma renin activity and plasma norepinephrine values were transformed to their logarithms. For these variables, geometric means and ranges are reported. Differences between treatment groups at randomization were tested by an unpaired Student's t test. The effects of antihypertensive treatment (and placebo in the run-out period) were tested by use of repeated measures analysis of variance. At each visit, the effect of treatment was compared with the results during the placebo period for the total study group. Between-group differences at each visit were compared with those differences at randomization by use of the contrast transformation. Furthermore, changes during active treatment were tested by comparing the averages of the 2 run-in visits with those of the data at 8 and 16 weeks (monotherapy), and at 38 and 52 weeks (end of active treatment). The latter data were used in regression analysis.[14,15] Differences in slopes between the 2 treatment groups were tested by use of a t test.[16] The 5% significance level was accepted as the criterion for statistical significance.

Reproducibility of the measurements: Reproducibility of the measurements was tested by comparison of the data obtained after 2 and 4 weeks of placebo treatment before randomization of the patients. The absolute and percent (absolute difference × 100/average of 2 measurements) within-patient differences of the repeated measurements were calculated. A 5 to 6% within-patient difference was found for systolic and diastolic BP measurements. The percent within-patient differences averaged 3 to 6% for LV structural measurements at end-diastole, 11% for fractional shortening of the LV internal diameter, 9% for stroke distance, and 7 to 13% for LV inflow characteristics. No systematic differences were observed.

RESULTS

Patients: Forty-one patients with essential hypertension entered the placebo run-in period. At the end of the run-in period BP was normal in 5 patients, and 4 did not comply with the protocol. Of the 32 randomized patients (whose characteristics are listed in Table I), 29

TABLE I Patient Characteristics at Randomization

	Isradipine Group	Lisinopril Group
No. of pts. (n)	16	16
Men/women (n)	9/7	10/6
Age (yr)	44 ± 7	38 ± 10
Body mass index (kg/m^2)	24.9 ± 2.6	26.1 ± 3.6
Supine BP (mm Hg)	160 ± 17/101 ± 11	159 ± 21/104 ± 14
Standing BP (mm Hg)	155 ± 19/105 ± 12	161 ± 22/112 ± 14
Supine heart rate (beats/min)	71 ± 9	71 ± 12
Serum creatinine (mg/dl)	0.98 ± 0.20	1.04 ± 0.22
Urinary sodium excretion (mmol/24 hours)	95 ± 41	82 ± 42
Previous antihypertensive treatment (yes/no; n)	9/7	7/9
Angiotensin-converting enzyme activity (U/ml)	34 ± 11	26 ± 13
Plasma renin activity (ng/ml/hour)	0.48 (0.01–3.36)	1.04 (0.06–4.06)
Plasma norepinephrine (ng/ml)	0.31 (0.18–0.56)	0.32 (0.12–0.52)

There were no significant differences between the groups ($p > 0.05$). Data are mean ± SD or geometric mean and range. BP = blood pressure.

completed the 1-year treatment period. In the isradipine group, 1 patient did not continue after randomization. In the lisinopril group, 1 subject was withdrawn after 4 weeks, because of hypotension on a low dose (5 mg) of the drug. These 2 patients were not considered in the analyses. Another patient in the lisinopril group refused further participation after 4 months of active treatment.

Treatment: The average daily dose of isradipine was 3.3 ± 1.2 mg at week 4, 5.7 ± 2.4 mg at week 8, and approximately 7.2 ± 3 mg from week 16 on, when hydrochlorothiazide (25 mg/day) was added in 8 patients. The dose of lisinopril averaged 9.7 ± 1.3 mg at week 4, 14.3 ± 5.6 at week 8, and between 19.7 ± 11.7 and 23.6 ± 13.9 mg from week 16 on; a diuretic was added in 1 patient at week 16 and in another at week 24.

Changes during active treatment: Body weight did not change significantly during 1-year follow-up.

BLOOD PRESSURE AND LEFT VENTRICULAR OUTFLOW CHARACTERISTICS: Systolic and diastolic BP decreased significantly during antihypertensive treatment ($p < 0.001$). The response differed between the 2 treatment groups at the beginning of the active treatment period, but was similar in the latter half of the study, except for a small difference in diastolic BP measured by the ob-

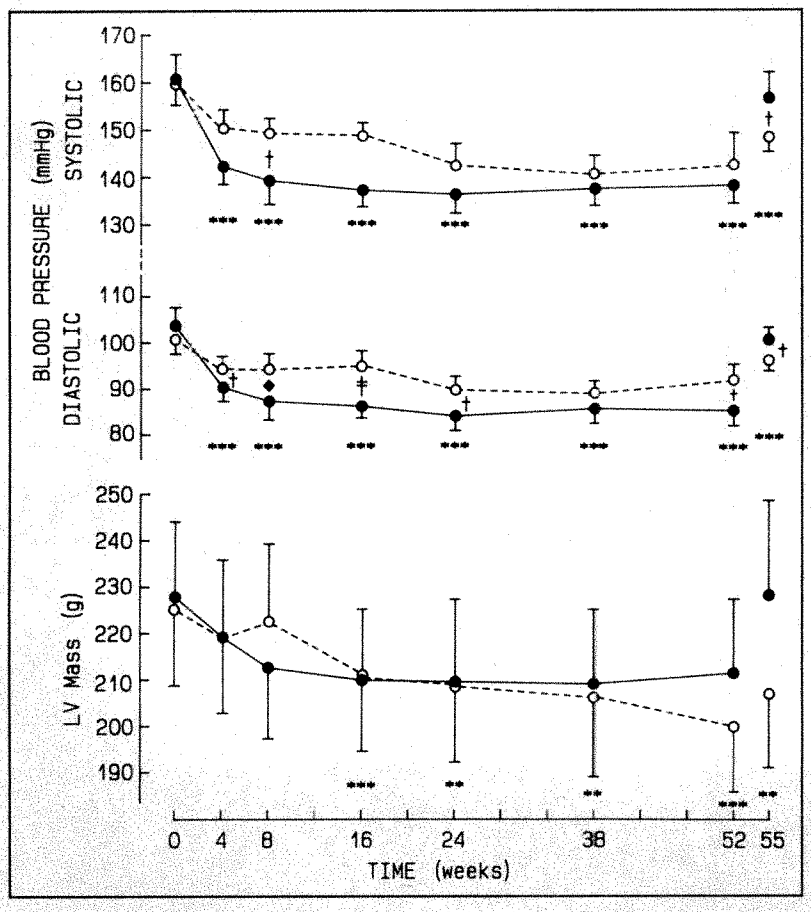


FIGURE 1. Blood pressure measured by observer, and left ventricular (LV) mass in both treatment groups as function of time of follow-up. Data are given as mean ± SE. *Open circles*, isradipine-based treatment group; *closed circles*, lisinopril-based treatment group; ** $p \leq 0.01$; *** $p \leq 0.001$ for the effect of treatment versus week 0 for all study patients; † $p \leq 0.05$, ‡ $p \leq 0.01$ and Δ $p \leq 0.001$ for the difference between the 2 treatment regimens versus that at week 0.

TABLE II Blood Pressure and Hemodynamic Characteristics Before and During Antihypertensive Treatment

		Run-In	During Active Treatment	F_t	F_c
Systolic/diastolic BP (mm Hg)					
Auscultatory	I	160 ± 16/101 ± 10	142 ± 17/91 ± 10	54.1*/55.4*	1.65/7.07†
	L	161 ± 19/105 ± 14	139 ± 13/86 ± 12		
Dinamap	I	153 ± 12/96 ± 8	137 ± 14/85 ± 7	50.3*/50.2*	0.94/3.37
	L	157 ± 16/98 ± 14	137 ± 11/82 ± 8		
Heart rate (beats/min)	I	71 ± 8	71 ± 11	0.07	0.06
	L	68 ± 9	68 ± 9		
Stroke distance (cm)	I	14.3 ± 4.4	15.1 ± 4.3	5.52†	0.34
	L	14.0 ± 3.9	14.6 ± 4.2		
Minute distance (m/min)	I	9.13 ± 3.4	9.72 ± 3.7	3.16	0.11
	L	8.81 ± 2.4	9.05 ± 2.8		
Linear resistance ($mm\ Hg/m \cdot min^{-1}$)	I	14.9 ± 5.4	12.7 ± 4.8	25.8*	0.41
	L	15.4 ± 6.0	12.9 ± 4.9		
No. of pts.	I	15	15		
	L	15	14		

*$p \leq 0.001$; †$p \leq 0.05$.
Data are mean ± SD.
BP = blood pressure; During Active Treatment = average of results at 38 and 52 weeks of active treatment; F_c = between-group differences in treatment effect; F_t = overall effect of treatment; I = isradipine-based treatment group; L = lisinopril-based treatment group; Run-In = average of results at 2 and 4 weeks of placebo treatment.

TABLE III Left Ventricular Structural and Functional Characteristics Before and During Antihypertensive Treatment

		Run-In	During Active Treatment	F_t	F_c
LV mass (g)	I	221.9 ± 62.8	203.0 ± 57.5	14.8*	0.09
	L	231.8 ± 62.8	210.1 ± 60.4		
Septal wall thickness, end-diastole (mm)	I	13.8 ± 2.10	12.2 ± 2.38	25.1*	0.74
	L	13.8 ± 3.63	13.0 ± 2.93		
Posterior wall thickness, end-diastole (mm)	I	12.3 ± 2.35	11.8 ± 2.20	3.72	0.00
	L	12.2 ± 2.68	11.5 ± 2.18		
Internal diameter, end-diastole (mm)	I	43.8 ± 4.72	44.6 ± 4.12	0.47	3.83
	L	45.7 ± 4.36	45.3 ± 4.38		
Relative wall thickness	I	0.60 ± 0.11	0.53 ± 0.10	17.26*	1.18
	L	0.58 ± 0.16	0.55 ± 0.12		
Fractional shortening (%)	I	36.6 ± 4.60	39.5 ± 7.00	9.43†	0.04
	L	33.4 ± 5.64	37.0 ± 5.63		
Wall stress (mm Hg)	I	56.9 ± 20.9	46.5 ± 15.1	18.37*	0.16
	L	62.7 ± 19.1	50.9 ± 13.1		
No. of pts.	I	15	15		
	L	15	14		

*$p < 0.001$; †$p < 0.01$.
LV = left ventricular; other abbreviations as in Table II.

server (Figure 1 and Table II). The increase in stroke distance was already significant after 8 weeks of treatment ($p < 0.01$). The decrease in linear resistance was significant from 4 weeks of treatment on ($p < 0.01$).

LEFT VENTRICULAR STRUCTURE: The overall change in LV mass was significant after 16 weeks of active treatment ($p < 0.001$) (Figure 1 and Table III). During this period of monotherapy, the decrease in LV mass was related to that in systolic BP ($r = 0.67$, $p < 0.001$). After the full active treatment period, LV mass had decreased on average by 20.0 ± 27.4 g ($p < 0.001$) and systolic BP by 20 ± 15 mm Hg ($p < 0.001$), without significant difference between the 2 treatment groups. For the total study group, the change in LV mass was related to that in systolic BP (Figure 2). The slope of the relation was 1.01 for the isradipine ($p = 0.01$) and 1.78 for the lisinopril ($p < 0.001$) groups; the difference between these slopes was not significant ($t = 1.68$, $p = 0.10$).

LEFT VENTRICULAR SYSTOLIC FUNCTION: From 4 weeks of treatment on, the increase in fractional shortening ($p < 0.05$), and decrease in wall stress ($p < 0.01$) were significant.

LEFT VENTRICULAR DIASTOLIC FUNCTION (TABLE IV): After the 16-week period of monotherapy, the A/E ratio calculated from the area under the Doppler curves decreased significantly ($p < 0.05$) without difference between the treatment groups. The decrease was already evident after 4 weeks ($p < 0.01$). After 1 year, changes in the A/E ratio were not significantly related to the decrease in BP or to the decrease in LV mass. Reduction in the A/E ratio was mainly due to an increase in the early diastolic inflow velocity and was similar in both groups.

TABLE IV Left Ventricular Inflow Characteristics Before and During Antihypertensive Treatment

		Run-In	During Active Treatment	F_t	F_c
A pV (cm/s)	I	47 ± 6.6	46 ± 6.5	0.52	0.13
	L	42 ± 7.3	42 ± 9.6		
A area (cm)	I	4.3 ± 0.67	4.1 ± 0.83	2.54	0.002
	L	3.8 ± 0.80	3.7 ± 0.96		
E pV (cm/s)	I	55 ± 12	57 ± 11	5.38*	1.75
	L	55 ± 11	60 ± 7		
E area (cm)	I	7.2 ± 1.79	7.7 ± 2.08	5.22*	0.005
	L	7.7 ± 1.18	8.1 ± 1.36		
A/E pV	I	0.89 ± 0.19	0.83 ± 0.17	5.76*	0.81
	L	0.79 ± 0.27	0.71 ± 0.18		
A/E area	I	0.63 ± 0.16	0.55 ± 0.13	7.70†	0.63
	L	0.50 ± 0.13	0.47 ± 0.18		
No. of pts.	I	15	15		
	L	15	14		

*$p < 0.05$; †$p < 0.01$.
A = atrial contraction phase; area = surface area under Doppler flow curve; E = early filling phase; pV = peak flow velocity; other abbreviations as in Table II.

BIOCHEMICAL DATA: At each visit on active treatment, plasma angiotensin-converting enzyme activity was significantly lower in the lisinopril than in the isradipine group ($0.0001 < p < 0.01$). After 1 year, angiotensin-converting enzyme activity remained unchanged (−1%) in the isradipine group and was reduced by 63% ($p < 0.001$) in the lisinopril group. The plasma norepinephrine level remained unchanged in each treatment group.

Changes during the three-week run-out period on placebo: Systolic and diastolic BP increased by 10 ($p < 0.001$) and 13% ($p < 0.001$), respectively, when active treatment was replaced by placebo treatment (Table V, Figure 1). The overall 15 mm Hg increase in systolic BP was associated with a 13 g increase in LV mass ($p < 0.01$). LV mass was not different from the pretreatment level in the lisinopril group, but was still significantly lower in the isradipine group ($p < 0.05$).

DISCUSSION

The present study indicates that the decrease of LV mass in patients with essential hypertension is similar in those treated with either lisinopril or isradipine (supple-

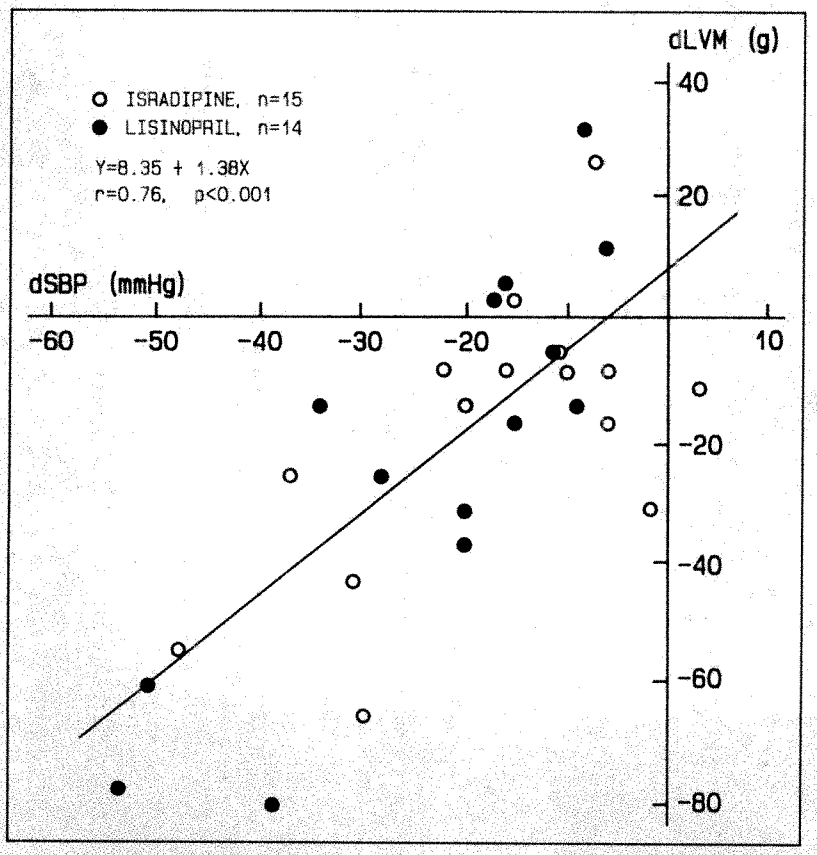


FIGURE 2. Relation between changes in left ventricular mass (dLVM) and in systolic blood pressure (dSBP) measured by observer during active antihypertensive treatment. *Open circles*, isradipine-based treatment group; *closed circles*, lisinopril-based treatment group.

TABLE V Blood Pressure, and Left Ventricular Structural, Functional and Inflow Characteristics at the End of the One-Year Antihypertensive Treatment Period and During the Placebo Run-Out Period

		End of Active Treatment	Run-Out	F_s	F_c
Systolic/diastolic BP (mm Hg)	I	144 ± 20/92 ± 12	149 ± 12/96 ± 8	40.8*/45.6*	4.85†/9.89‡
	L	139 ± 15/86 ± 11	158 ± 19/101 ± 10		
LV structure and function					
Mean wall thickness, end-diastole (mm)	I	11.8 ± 2.0	12.1 ± 2.0	5.60†	0.48
	L	12.2 ± 2.4	12.6 ± 2.8		
Internal diameter, end-diastole (mm)	I	45 ± 4.2	44 ± 5.3	1.82	1.18
	L	45 ± 4.6	46 ± 4.2		
LV mass (g)	I	200 ± 59	207 ± 57	9.85‡	1.17
	L	209 ± 63	228 ± 73		
Fractional shortening (%)	I	40 ± 7.2	37 ± 7.3	4.26†	1.81
	L	37 ± 5.8	36 ± 5.9		
Wall stress (mm Hg)	I	45 ± 16	53 ± 19	7.73‡	0.06
	L	51 ± 14	60 ± 16		
LV inflow					
A/E pV	I	0.84 ± 0.17	0.90 ± 0.23	1.24	0.05
	L	0.70 ± 0.18	0.74 ± 0.24		
A/E area	I	0.57 ± 0.13	0.59 ± 0.15	0.19	0.68
	L	0.47 ± 0.19	0.46 ± 0.16		
No. of pts.	I	14	14		
	L	13	13		

*$p \leq 0.001$; †$p \leq 0.05$; ‡$p \leq 0.01$.
Data are mean ± SD.
End of Active Treatment = results at 52 weeks active treatment; F_s = overall effect of stopping of active treatment; Run-out = results at 3 weeks placebo treatment; other abbreviations as in Tables II to IV.

mented with a diuretic, if necessary). The hypotensive effects of both regimens were comparable and based on a reduction in systemic vascular resistance. Minute distance in the ascending aorta (Doppler index of cardiac output) remained unchanged throughout the treatment period.

During monotherapy and at the end of the active treatment period, the change in LV mass from the initial control value was significantly related to that in BP; furthermore, the slope of the relations between changes in LV mass and BP was not significantly different in the 2 treatment groups. These findings suggest that the reduction in BP is a major determinant of the regression of LV mass and that the mechanisms by which BP is lowered with these treatment regimens may be of less importance. It has been suggested that angiotensin-converting enzyme inhibitors are particularly effective in reducing LV mass, because angiotensin II is thought to be involved in the development of LV hypertrophy.[17,18] There is no doubt that angiotensin II can indeed be a growth factor[6] triggering protein synthesis. However, it should be recognized that at least the plasma renin angiotensin system is on average not stimulated in essential hypertension.[19] Therefore, it is not surprising that the reduction in LV mass is similar whether or not the angiotensin II generation is suppressed. Diuretics were more often prescribed in isradipine-treated patients, but this could only have increased differences in the renin-angiotensin system activity between the 2 groups.[20,21] It is difficult to reach an unequivocal conclusion from this study on the role of the renin-angiotensin system in LV hypertrophy, because the activity of the tissue renin-angiotensin system could not be assessed. However, angiotensin-converting enzyme inhibition has been shown to decrease the cardiac tissue angiotensin II.[22] It is noteworthy that a 3-week interruption of active treatment led to a significant increase in LV mass. This increase was more pronounced in the lisinopril- than isradipine-treated patients, which coincides with the steeper increase of BP in the lisinopril group. Other investigators reported a decrease in LV mass during chronic treatment with an angiotensin-converting enzyme inhibitor[18,23–25] or calcium-antagonist[21,26] in patients with essential hypertension, and a significant increase in LV mass was reported[24] after treatment with perindopril had been interrupted for 4 weeks.

It is generally accepted that LV systolic function is not (or only minimally) affected in moderate essential hypertension.[1] However, the present long-term antihypertensive treatment was associated with a small but significant increase in fractional shortening of the LV internal diameter. This is most likely due to the reduction in LV wall stress and does not necessarily imply an improved intrinsic contractility. Similar data were reported in black hypertensive patients treated with isradipine.[26]

LV diastolic function as assessed by LV Doppler velocimetry is impaired in hypertension.[2–4] It is not clear whether this is predominantly related to the increased BP or LV mass.[27,28] Shahi et al[25] could not show a change of diastolic function (as assessed by Doppler velocimetry) after 9 to 18 months of treatment with captopril. In contrast, we observed a significant reduction in the Doppler-derived A/E ratio after 4 weeks of treatment when BP (but not LV mass) was significantly lower than during the run-in period, suggesting that BP or related factors are at least partly involved. Correlation analysis did not allow further conclusions.

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Characteristics of Peak Aerobic Capacity in Symptomatic and Asymptomatic Subjects with Left Ventricular Dysfunction

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Expired gas analysis was used to determine the aerobic exercise performance of subjects with depressed left ventricular (LV) systolic function and congestive heart failure (CHF). To determine whether subjects with no or minimal CHF have better aerobic exercise performance than do those with overt CHF, oxygen consumption ($\dot{V}O_2$) at anaerobic threshold (AT) and peak exercise was measured in 184 subjects with LV ejection fraction ≤0.35 who participated in the Studies of Left Ventricular Dysfunction. Subjects were divided into those with overt CHF needing treatment (treatment trial; n = 20) and those who had neither overt CHF nor treatment for CHF (prevention trial; n = 164). Treatment trial subjects had a lower LV ejection fraction (0.25 ± 0.07) than did prevention trial ones (0.29 ± 0.05; p = 0.001), but there were no differences in age, gender, body weight, resting heart rate and blood pressure. Treadmill exercise testing was performed after 2 to 3 weeks of placebo (no angiotensin-converting enzyme inhibitor) treatment. Treatment trial subjects exercised for a shorter time (493 ± 160 seconds) and attained a lower peak $\dot{V}O_2$ (13 ± 4 ml/kg/min) and $\dot{V}O_2$ at AT (11 ± 4 ml/kg/min) than did prevention trial ones (842 ± 277 seconds, and 20 ± 6 and 16 ± 5 ml/kg/min, respectively). Analysis of covariance showed that the differences in peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT were statistically significant between the 2 trials after adjusting for age, gender, LV ejection fraction and New York Heart Association functional class. In contrast, there was no correlation between the expired gas measurements and LV ejection fraction or New York Heart Association classification after adjusting for other factors. Thus, it is concluded that of subjects with reduced LV ejection fraction, those with no or minimal CHF have higher aerobic exercise performance than do those with overt CHF, and this difference cannot be explained by gender, age, LV ejection fraction or New York Heart Association functional class.

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Noninvasive measurements of expired gas during graded exercise, and determination of peak oxygen consumption (peak $\dot{V}O_2$) have greatly advanced our knowledge of the cardiopulmonary and metabolic responses to maximal exercise in normal subjects.[1,2] Such measurements have also been used to assess the functional capacity of subjects with congestive heart failure (CHF) in single center studies.[3,4] However, whether measurements of respiratory gas exchange are equally helpful in determining the functional status of a large number of subjects enrolled in a broad clinical trial has yet to be validated.

The Studies of Left Ventricular Dysfunction (SOLVD) of the converting enzyme inhibitor enalapril included 2 different populations with CHF.[5] The treatment trial included subjects with left ventricular (LV) ejection fraction ≤0.35 and symptoms needing specific therapy for CHF. Enalapril reduced the mortality and hospitalization rates in these patients.[6] The prevention trial included subjects with LV ejection fraction ≤0.35, but with no or minimal symptoms, as defined by the absence of specific therapy for CHF. To study whether peak exercise oxygen performance was greater in subjects with no or minimal symptoms than in those treated for symptoms of CHF, 5 SOLVD clinical centers systematically measured peak aerobic capacity using expired gas analyses[7,8] before randomization to enalapril or placebo.

METHODS

Subjects: Subjects were recruited using a standardized protocol[5] from June 1988 to May 1990. The study conformed with the Declaration of Helsinki for studies involving human subjects and was approved by human study review boards. Subjects had an LV ejection frac-

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TABLE I Clinical Characteristics of Treatment and Prevention Trials

	Treatment	Prevention	p Value
Women/men	2/18	24/140	
Age (yr)	59 ± 9 (20)	58 ± 10 (164)	0.655
Body weight (kg)	81 ± 15 (20)	81 ± 14 (164)	0.998
Body mass index (kg/m^2)	27 ± 5 (20)	27 ± 4 (164)	0.848
Standing blood pressure (mm Hg)			
Systolic	131 ± 21 (20)	130 ± 19 (162)	0.802
Diastolic	79 ± 6 (20)	82 ± 11 (162)	0.278
Standing heart rate (beats/min)	84 ± 17 (20)	83 ± 18 (161)	0.764
LV ejection fraction	0.25 ± 0.07 (20)	0.29 ± 0.05 (164)	<0.001
Cardiothoracic ratio (%)	53 ± 5 (9)	49 ± 7 (127)	0.057
NYHA functional class			<0.010
I	3 (15%)	114 (70%)	
II	9 (45%)	50 (30%)	
III	8 (40%)	0	
Cause of LV dysfunction			<0.010
Ischemic	10 (50%)	139 (85%)	
Idiopathic	2 (10%)	16 (10%)	
Other	8 (40%)	9 (5%)	

Values are mean ± SD. Numbers of subjects studied are shown in parentheses. p values indicate statistical levels of significance for differences between treatment and prevention trial subjects. Causes of LV dysfunction under "Other" include: hypertensive heart disease in 2 prevention and 4 treatment trial subjects; alcoholic heart disease in 1 prevention and 1 treatment trial subject; hypertensive and alcoholic heart diseases in 1 prevention and 2 treatment trial subjects; valvular pathology in 1 treatment and 2 prevention trial subjects; viral myocarditis in 1 prevention trial subject; cardiac trauma in 1 prevention trial subject; and rheumatic heart disease in 1 prevention trial subject.
LV = left ventricular; NYHA = New York Heart Association.

tion ≤0.35 within 3 months of the day of consent, and were aged between 21 and 80 years. Ejection fraction was assessed by radionuclide ventriculography, contrast angiography or 2-dimensional echocardiography using the area–length method or Simpson's rule. In addition to meeting all inclusion and exclusion criteria of the SOLVD study,[5] subjects recruited into the exercise substudy also had no mental obtundation, orthostatic symptoms, dyspnea at rest, noncardiac functional limitation such as limiting pulmonary, musculoskeletal or peripheral vascular disease, or exercise-limiting angina pectoris. One hundred sixty-four prevention trial subjects were studied. However, because this study was initiated when recruitment to the treatment trial was mostly complete, only 6 treatment trial subjects were available for the substudy. In subsequent months, we recruited another 14 subjects who met all eligibility criteria. These 20 subjects formed the substudy treatment trial. The 164 substudy prevention trial subjects represented 42% of those randomized to the SOLVD prevention trial in the 5 centers during the exercise substudy enrollment period.

Treadmill exercise test: Subjects underwent a baseline treadmill exercise test after 2 to 3 weeks of placebo treatment.[5] They began the exercise test standing on a treadmill, with gas exchange monitored using either a Medical Graphics System 2001 or Sensor-Medics 4400 capable of real-time single-breath analysis of expired gas. After a rest period of ≥2 minutes, exercise testing was begun using a modified Naughton protocol.[9] Treadmill speed and grade were adjusted to produce stepwise increases in work load every 2 minutes. Subjective sensation of perceived exertion was recorded using a modified Borg rating scale[10] with 10 as the highest score. Exercise was discontinued when the patient was unable to maintain the imposed work load as manifested by inability to consistently maintain speed on the treadmill, or by development of significant exercise-induced hypotension, chest pain, ventricular tachycardia or marked ST-segment depression. The electrocardiogram was monitored continuously. Blood pressure was determined using cuff plethysmography. Data were sent to the exercise substudy core laboratory at the University of Rochester Medical Center, Rochester, New York, for uniform determination of peak $\dot{V}O_2$ and oxygen consumption at anaerobic threshold (AT), a measure of submaximal exercise capacity.[8,11] Peak $\dot{V}O_2$ was determined as the highest $\dot{V}O_2$ achieved during exercise and was normalized by either body weight (kg) or mass index, defined as the ratio of body weight and squares of height (kg/m^2). AT was the point in time when there was a systematic increase in ventilatory equivalent of oxygen.[3,8] Other associated changes at AT included systematic increases in end-tidal oxygen partial pressure and respiratory exchange ratio.[3,8,11,12]

Statistics: Experimental results are reported as mean ± SD. The statistical significance of differences between the groups was determined using analysis of variance, and Student's *t* test with Bonferroni correction. The interrelations between peak $\dot{V}O_2$, peak exercise heart rate, peak oxygen pulse ($\dot{V}O_2$/heart rate), age, gender, LV ejection fraction and New York Heart Association functional class were studied using correlation. Analysis of covariance was then performed to determine if the differences in peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT were still statistically significant after adjusting for age, gender, New York Heart Association functional class and LV ejection fraction. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Demographic and clinical characteristics: The demographic profile and clinical characteristics of the study groups are shown in Table I. There were no statis-

TABLE II Peak Exercise Performance in Treatment and Prevention Trials

	Treatment	Prevention	p Value
Exercise duration (sec)	493 ± 160 (20)	842 ± 277 (164)	<0.0001
Peak $\dot{V}O_2$			
ml/kg/min	13 ± 4 (20)	20 ± 6 (164)	<0.0001
ml/BMI/min	37 ± 11 (20)	60 ± 21 (164)	<0.0001
Peak heart rate (beats/min)	128 ± 23 (20)	145 ± 23 (162)	<0.002
Peak systolic pressure (mm Hg)	154 ± 29 (18)	166 ± 24 (164)	0.052
Peak oxygen pulse (ml/beat)	8 ± 3 (20)	11 ± 4 (162)	<0.0002
Time to AT (sec)	331 ± 156 (13)	573 ± 211 (148)	<0.0001
$\dot{V}O_2$ at AT			
ml/kg/min	11 ± 4 (13)	16 ± 5 (148)	<0.0004
ml/BMI/min	32 ± 11 (13)	49 ± 16 (148)	<0.0001
Highest Borg score	7.9 ± 2.5 (15)	7.7 ± 2.3 (163)	0.820
Peak respiratory exchange ratio	1.09 ± 0.13 (20)	1.11 ± 0.13 (164)	0.337

Values are mean ± SD. Numbers of subjects are given in parentheses. p values indicate statistical levels of significance for differences between treatment and prevention trial subjects as determined by analysis of variance.
AT = anaerobic threshold; BMI = body mass index (kg/m^2); $\dot{V}O_2$ = oxygen consumption.

tical differences in gender, age, body weight and mass index, standing arterial blood pressure and heart rate at rest between treatment and prevention trial subjects. Treatment trial subjects had a lower LV ejection fraction than did prevention trial ones, but the difference in cardiothoracic ratio was not statistically significant. Seventy percent of prevention trial subjects were in New York Heart Association class I, with the remainder in class II. In contrast, most subjects in the treatment trial were symptomatic in New York Heart Association classes II and III. The cause of LV dysfunction was ischemic in most subjects in both trials; proportionately more in the treatment trial had nonischemic causes.

Exercise performance: Exercise testing was discontinued because of dyspnea or fatigue in 139 prevention (85%) and 18 treatment (90%) trial subjects. The other reasons for discontinuation of exercise included chest pain (1 treatment and 6 prevention trial subjects), ventricular tachycardia (2 prevention trial), marked ST-segment depression (1 prevention trial), hypotension (1 prevention trial), and others (1 treatment and 15 prevention trial) such as dry mouth, leg pain, dizziness and arm pain.

Table II shows that treatment trial subjects had a shorter exercise duration and a lower peak $\dot{V}O_2$ than did prevention trial ones. The lower peak $\dot{V}O_2$ in the treatment trial was associated with a similarly reduced peak exercise heart rate, oxygen pulse, time to AT, and $\dot{V}O_2$ at AT. Peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT differed between the 2 trials irrespective of normalization by body weight or mass index. However, there was no difference in peak systolic blood pressure, Borg score or respiratory exchange ratio achieved at end of exercise.

Relation between clinical variables and exercise performance: Peak $\dot{V}O_2$ correlated significantly with age ($r = -0.35$, $p < 0.0001$), gender ($r = 0.26$, $p < 0.001$) and New York Heart Association functional class ($r = -0.32$, $p < 0.0001$). Significant correlations were also present between $\dot{V}O_2$ at AT and age ($r = -0.29$, $p < 0.001$), gender ($r = 0.31$, $p < 0.0001$) and New York Heart Association functional class ($r = -0.24$, $p < 0.001$). However, neither peak $\dot{V}O_2$ nor $\dot{V}O_2$ at AT correlated significantly with LV ejection fraction ($r = 0.07$).

Analysis of covariance was used to determine if peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT between the treatment and prevention trials differed after adjusting for age, gender, New York Heart Association functional class and LV ejection fraction. Two-way interactions were also included to ascertain if differences in peak $\dot{V}O_2$ or $\dot{V}O_2$ at AT on 1 factor (i.e., gender) were constant over all levels of another (i.e., LV ejection fraction). None of the interactions were statistically significant, so they were excluded from analysis. Differences in peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT were significant ($p < 0.005$) between the prevention and treatment trials after adjusting for age, gender, LV ejection fraction and New York Heart Association functional class. Gender and age were also significant ($p < 0.0001$) after adjusting for all other factors. However, neither LV ejection fraction nor New York Heart Association classification affected exercise gas measurements after other factors had been adjusted. Furthermore, neither peak $\dot{V}O_2$ nor $\dot{V}O_2$ at AT differed between the prevention trial subjects treated with and without β-receptor or those receiving no calcium antagonists. In subjects receiving no β-receptor or calcium antagonist, peak $\dot{V}O_2$ values were 21 ± 7 and 21 ± 7 ml/kg/min, respectively, which did not differ significantly from those who received the blocking agents.

Effect of age: Peak $\dot{V}O_2$ correlated significantly with age in all subjects ($r = -0.35$, $p < 0.0001$). The correlation coefficient was significant in the prevention trial ($r = -0.39$, $p < 0.0001$), but perhaps because of the small number of subjects and narrow age range, did not reach statistical significance in the treatment trial.

Effect of gender: Table III shows that although there was no difference in age or LV ejection fraction between men and women in the prevention trial, women exercised for a shorter duration and attained a lower peak $\dot{V}O_2$, $\dot{V}O_2$ at AT and peak oxygen pulse than did men. Time to AT was also shorter in women, but the 2 groups did not differ in peak exercise heart rate, blood

TABLE III Differences in Peak Exercise Performance Between Men and Women

	Prevention Trial		Treatment Trial
	Men	Women	Men
Pt. no.	140	24	18
Age (yr)	58 ± 10	58 ± 12	59 ± 9
LV ejection fraction	0.29 ± 0.05	0.29 ± 0.06	0.25 ± 0.07*
Exercise duration (sec)	875 ± 277	638 ± 175†	503 ± 163†
Peak $\dot{V}O_2$			
ml/kg/min	21.0 ± 6.3	15.4 ± 4.6†	12.7 ± 4.3†
ml/BMI/min	64.5 ± 20.5	40.3 ± 12.7†	37.8 ± 11.6†
Peak heart rate (beats/min)	146 ± 22	136 ± 24	128 ± 24†
Peak systolic pressure (mm Hg)	166 ± 23	166 ± 29	156 ± 30
Peak oxygen pulse (ml/beat)	11.8 ± 3.6	8.1 ± 2.4†	8.0 ± 2.8†
$\dot{V}O_2$ at AT			
ml/kg/min	16.9 ± 4.7	11.6 ± 3.6†	10.9 ± 4.2†
ml/BMI/min	51.7 ± 15	30.4 ± 9.3†	32.9 ± 11.1†
Time to AT (sec)	597 ± 209	415 ± 143†	337 ± 159†
Highest Borg score	7.5 ± 2.3	8.3 ± 2.1	7.9 ± 2.6
Peak respiratory exchange ratio	1.12 ± 0.13	1.06 ± 0.10	1.10 ± 0.13

*$p < 0.05$, †$p < 0.01$ compared with men in prevention trial using analysis of variance, and Bonferroni t test.
Values are mean ± SD. Numbers of subjects who reached anaerobic threshold (AT) were 129, 19 and 12 for prevention trial men and women, and treatment trial men, respectively.
Abbreviations as in Tables I and II.

pressure, respiratory exchange ratio or end of exercise Borg score.

Compared with men in the prevention trial, those in the treatment trial had a lower LV ejection fraction and peak exercise performance (as evidenced by the shorter exercise duration), and reduced peak exercise heart rate, $\dot{V}O_2$ and oxygen pulse, $\dot{V}O_2$ at AT and time to AT (Table III). However, there was no significant difference in peak systolic blood pressure, highest Borg score or peak respiratory exchange ratio.

Effect of cause of left ventricular dysfunction: Peak $\dot{V}O_2$ did not differ between subjects with ischemic and nonischemic heart disease in either the prevention or treatment trial (Figure 1), nor did it correlate significantly with cause of LV dysfunction in the pooled data ($r = 0.027$, $p = 0.75$).

DISCUSSION

The present study characterizes the prevention and treatment trials of the SOLVD subjects by exercise capacity. Treatment trial subjects were distinguished from prevention trial ones by the need for treatment of CHF with digitalis or diuretics, or both. Treatment trial subjects also had a lower LV ejection fraction and a higher New York Heart Association class than did prevention trial ones. Furthermore, prevention trial subjects had less neuroendocrine activation than did treatment trial ones.[13] This report shows that prevention trial subjects have a greater exercise capacity than do treatment trial ones. Results of our study further indicate that the differences in peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT between the 2 trials cannot be explained by differences in age, body mass index, gender, New York Heart Association functional class, LV ejection fraction or cause of LV dysfunction alone. Absence of correlation between LV ejection fraction and peak $\dot{V}O_2$ or $\dot{V}O_2$ at AT was previously demonstrated for subjects with CHF.[14–17] However, to our knowledge, the exercise oxygen performance of this large group of asymptomatic or minimally symptomatic subjects with severe LV dysfunction is unique in the literature and was not previously reported.

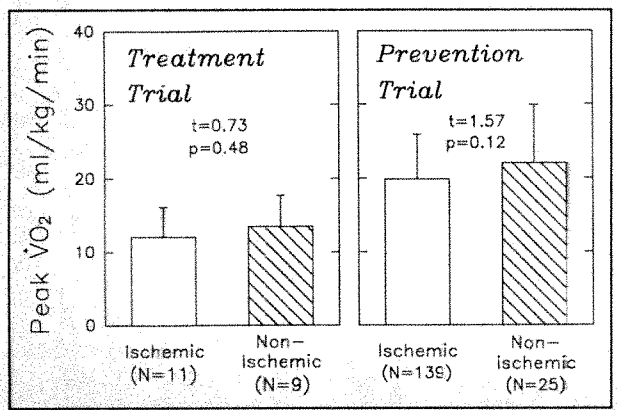


FIGURE 1. Differences in peak oxygen consumption ($\dot{V}O_2$) between prevention and treatment trial subjects divided according to ischemic and nonischemic causes. Peak oxygen consumption did not differ between the 2 groups of subjects.

Peak $\dot{V}O_2$ differed between the prevention and treatment trials in our study. These values were significantly lower than the normal ones obtained in a group of concurrent control subjects.[18] Prevention trial subjects achieved a mean peak $\dot{V}O_2$ that corresponds to Weber classes A and B,[9] or Franciosa classes I and II.[14] However, treatment trial subjects had a peak $\dot{V}O_2$ that corresponds to Weber class C or Franciosa class III. The results of the treatment trial subjects are comparable to those reported recently by Elkayam et al[19] in subjects with New York Heart Association class III and IV CHF.

A decrease in peak $\dot{V}O_2$ with age is known and correlates with a reduction in peak heart rate. The lower peak $\dot{V}O_2$ in women than in men has also been reported.[20,21] The gender differences in peak $\dot{V}O_2$ did not disappear after normalization by body weight or mass index, nor could it be explained by progesterone, because peak $\dot{V}O_2$ was not reduced by progesterone.[22]

This study has a few potential limitations. First, exercise studies were performed in 5 separate laboratories. However, the methodology was standardized, and all data were analyzed in a core laboratory. Second, only a small number of treatment trial subjects were enrolled, because the exercise substudy began near the end of completion of enrollment for the treatment arm of the SOLVD program. Third, not all prevention trial subjects were completely asymptomatic; more precisely, they differed from the treatment trial subjects in that they did not need digoxin and diuretics for CHF. Fourth, the New York Heart Association classification is based on patients' general functional status, which could be limited not only by cardiac systolic dysfunction, but also by underlying pathology such as coronary artery disease. Exercise-induced myocardial ischemia could have limited the patients' exercise performance. However, most subjects stopped exercise because of dyspnea and fatigue; only 10 (5%) developed chest pain, ST-segment changes or ventricular tachycardia during exercise, suggesting that myocardial ischemia probably was not the major cause for discontinuation of exercise.

Thus, the methodological limitations do not affect our major conclusion that asymptomatic or mildly symptomatic subjects have a greater aerobic exercise capacity than do symptomatic ones needing digoxin or diuretics. Furthermore, the difference in peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT between the 2 groups of subjects cannot be explained by differences in age, gender, LV ejection fraction, New York Heart Association functional class or cause of LV dysfunction. The findings suggest that the appearance of symptoms in subjects with LV dysfunction may reflect an unmeasured or unmeasurable entity that confers symptomatic status and limits peak $\dot{V}O_2$. Recently, right ventricular function was speculated to have an important role in determining the functional capacity of patients with chronic LV failure.[23] However, right ventricular ejection fraction did not correlate with either maximum $\dot{V}O_2$[24] or upright bicycle work load (Kronenberg et al, unpublished data). Reasons for the differences between symptomatic and asymptomatic subjects with LV dysfunction remain to be determined.

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Long-Term Outcome in Patients with Congestive Heart Failure and Intact Systolic Left Ventricular Performance

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Congestive heart failure (CHF) is typically associated with impaired left ventricular (LV) systolic performance. Few reports exist describing the long-term outcome in patients with CHF and normal LV systolic function. Fifty-two patients initially hospitalized with CHF and intact LV function (ejection fraction ≥45%) were followed for 7 years. Mean age when initially identified was 71 ± 11 years (range 36 to 96), and average LV ejection fraction was 61 ± 11%. CHF was graded by a clinicoradiographic index, with a mean of 7.0 ± 2.3 (range 3 to 12, 13 indicates worst CHF). A third heart sound was present in 19 patients (37%), and 17 (33%) had presented with acute pulmonary edema. Principal cardiovascular diagnoses were coronary artery disease in 27 (52%), hypertensive heart disease in 16 (31%) and restrictive cardiomyopathy in 7 (13%). At 7 years, cardiovascular mortality was 46% (24 of 52), and noncardiovascular mortality was 10% (5 of 52). Survival was not correlated with age, principal diagnosis, third heart sound, pulmonary edema at presentation, LV ejection fraction, or presence or degree of LV diastolic dysfunction. Cardiovascular morbidity, consisting of nonfatal recurrent CHF, myocardial infarction, unstable angina or other cardiovascular events occurred in 29% (15 of 52). Combined cardiovascular mortality and morbidity was 75% (39 of 52). In patients with CHF, intact LV systolic function does not confer the same favorable prognosis it defines in other clinical situations. For such patients, the risk of future cardiovascular events is high, a finding that should be considered when designing therapeutic strategies in this group.

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Left ventricular (LV) ejection fraction exerts a major influence on prognosis in a variety of cardiac conditions.[1–10] LV function as assessed by radionuclide ejection fraction has been useful in defining subsets of patients with congestive heart failure (CHF) and a poor long-term outcome. Clinical CHF, irrespective of etiology, carries a 5-year mortality ≥50% in most series.[2,3,6,9,11–17] Within many series, there is an inverse relation between LV function and mortality.[2,6–10] The patient cohort with classic CHF and preserved LV ejection fraction has been well described,[18–20] and may consist of 30 to 40% of patients presenting with CHF. Common clinical correlates include coronary artery disease, systemic hypertension and restrictive cardiomyopathy.[20] To describe the long-term outcome in such patients, we obtained 7-year follow-up data in 58 patients previously identified with CHF and preserved LV systolic function.[20]

METHODS

Patient population: The original population was referred to the nuclear cardiology laboratory at Yale-New Haven Hospital and the West Haven Veterans Administration Medical Center, as described previously.[20] Screening was conducted for 1 year, from 1981 to 1982. Patients were selected who had a diagnosis of CHF with an LV ejection fraction ≥45%, the normal value for our laboratory. The initial group consisted of 58 patients. Then CHF was graded by an experienced cardiologist using a clinicoradiographic scale of 0 to 13 (13 indicates the most severe CHF).[20,21] Dyspnea and physical and roentgenographic signs of CHF were scored: 1 point was given for mild to moderate dyspnea on exertion, 2 for severe dyspnea on exertion or paroxysmal nocturnal dyspnea, 3 for orthopnea, and 4 for dyspnea at rest. Basilar rales rated 1 point, 2 if above the bases. A third heart sound merited 2 points if present, 0 if absent. More than 6 cm of jugular venous pressure was given 1 point, 2 for pedal edema or hepatosplenomegaly. On chest radiography, 1 point was given for pulmonary vascular redistribution, 2 for interstitial edema, 3 for alveolar edema, or interstitial edema with pleural effusions. All patients had a high temporal resolution nuclear probe study to evaluate LV diastolic filling.[22,23] Peak filling rate, normalized to end-diastolic volume, was chosen as the parameter of diastolic function (≥2.5 end-diastolic volumes/second is normal).[20]

Patient follow-up: In 1989, after approval by the Human Investigation Committee, all patients were followed by review of hospital charts with postmortem results, clinic and physicians' office records, cardiac catheterization and surgical reports, and interviews with physicians, patients and surviving relatives. Fifty-two hospital or clinic charts and 10 catheterization or cardiac surgical reports were evaluated, and 39 interviews conducted. Death was classified as cardiovascular in nature when medical descriptions confirmed that CHF, myocardial infarction, cerebrovascular accident, arrhythmia or sudden death (within 2 hours of appearance of symptoms) were fully implicated in the patient's death. Cardiovascular morbidity was defined as a nonfatal event requiring hospitalization, including pulmonary edema, myocardial infarction, unstable angina, cerebrovascular accident or symptomatic arrhythmia.

Statistical analysis: Data are expressed as mean ± SD. A p value <0.05 was considered significant, and survival was plotted using Kaplan-Meier life-table analysis.[24] Though numbers of patients were small, we evaluated factors that may be associated with morbidity and mortality using Cox regression analysis and Pearson's chi-square test.[25]

RESULTS

Clinical characteristics: Characteristics of the initial group of 58 patients have been reviewed.[20] Of the original 58, follow-up was obtained in 52 (90%). There were 27 women and 25 men. Mean age at entry was 71 ± 11 years. Average LV ejection fraction in 1982 was 61 ± 11% (range of 45 to 91%). Mean peak filling rate was 2.97 ± 0.14 end-diastolic volumes/second (range 0.99 to 7.20). CHF score for the follow-up group was 7.0 ± 2.3 (range 3 to 12).[20,21] All patients had New York Heart Association class III to IV CHF. A third heart sound had been present in 19 patients (37%) of the follow-up group. Acute pulmonary edema had originally been noted in 17 patients (33%). Cardiovascular diagnoses consisted of coronary artery disease in 27 (52%), hypertensive heart disease in 16 (31%) and restrictive cardiomyopathy in 7 (13%). In 2 (4%) the underlying diagnosis was unclear. Clinically, the follow-up group of 52 patients did not differ significantly from the original 58.

Morbidity: Among survivors and nonsurvivors, 28 (54%) had recurrent CHF, and 5 (10%) had angina or required coronary artery bypass surgery. Nonfatal cardiovascular morbidity alone occurred in 15 (29%), myocardial infarction in 4 (8%), and 2 (4%) had other events such as stroke or severe arrhythmia. Although most patients were receiving digoxin and diuretics at entry, we have not reported the subsequent pharmacotherapy of the cohort because of the difficulty in judging the effects of multiple agents given for varying intervals.

Mortality: After 7 years, 24 patients (46%) died of cardiovascular causes. Thus, cumulative survival of the study group with respect to cardiovascular mortality alone was 54% (Figure 1). As listed later, most patients dying of cardiovascular causes had severe recurrent or intractable CHF, in some cases associated with other diseases, such as hypertension or amyloidosis, which predisposed them to diastolic heart failure.

Recurrent refractory CHF caused death in 6 patients, and 2 died after attempted cardiopulmonary resuscitation for sudden pulmonary edema, without observed arrhythmias. Pulmonary edema with probable pneumonia caused the deaths of 2 patients: 1 died from pulmonary edema and rapid atrial fibrillation, and 1 patient died with pulmonary edema during general surgery. Pulmonary edema with end-stage systemic sclerosis caused death in 1 patient, and 2 died with CHF and end-stage amyloidosis, 1 with CHF and pericarditis, and 1 died with CHF with a non-Q-wave myocardial

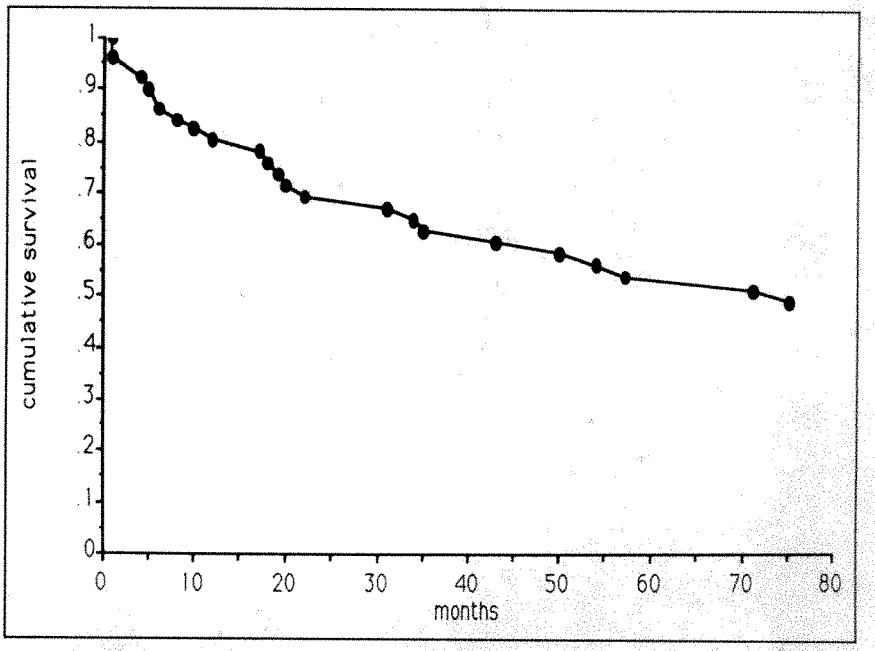


FIGURE 1. Survival curve for patients with clinical congestive heart failure and intact left ventricular systolic function. Fraction of original cohort surviving is displayed on the *y axis*, and time in months on the *x axis*.

infarction and sepsis. Another died with CHF complicating chronic obstructive airways disease, and 1 died with CHF and hypertension during renal dialysis. Fatal Q-wave myocardial infarctions occurred in 2 patients, 1 died of a hypertensive cerebrovascular accident, 1 died with hypertrophic cardiomyopathy complicated by myocardial infarction and severe mitral regurgitation, and 1 patient died of intractable postoperative CHF after valve replacement for mixed aortic valvular disease. Noncardiovascular etiologies caused death in 5 patients (10%), including variceal hemorrhage, gynecologic neoplasm, seizure with aspiration pneumonia and renal failure; in 1 the cause of death was uncertain.

Mean survival time was 53.7 ± 4.7 months. Median survival time was 35 months. Combined cardiovascular mortality and morbidity occurred in 39 patients (75%) at 7 years (Figure 2). Survivors continued to experience morbid events even through the final 2 years of follow-up (Figure 2). Most early morbidities resulted in mortality and are illustrated as such in the combined curve (Figure 2).

Follow-up radionuclide angiocardiography: Repeat assessment of LV ejection fraction was performed in 13 patients during the follow-up period. We reviewed these limited data to determine if some adverse outcomes might be linked to deteriorating LV function. In 5 patients, LV ejection fraction decreased to <45% (from 61 ± 12% to 36 ± 6%): 3 of these patients died, and 2 were alive at follow-up, though both had cardiovascular events. In 8 patients, LV ejection fraction remained nor-

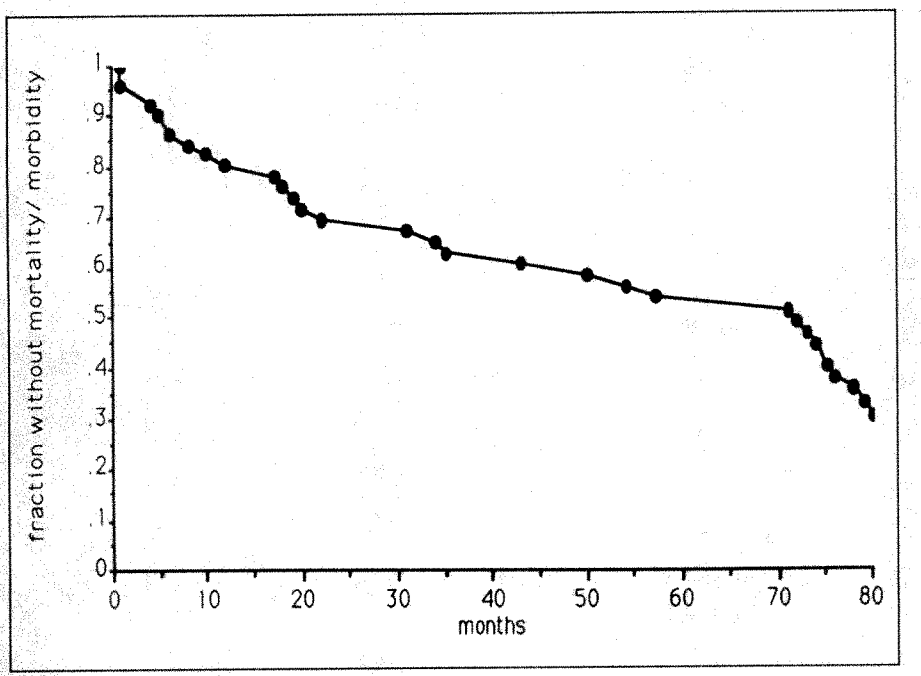


FIGURE 2. Curve demonstrating combined cardiovascular mortality and morbidity during the follow-up period for patients with clinical congestive heart failure and intact left ventricular systolic function. Fraction of original cohort free of cardiovascular mortality and morbidity is displayed on the *y axis*, and time in months on the *x axis*.

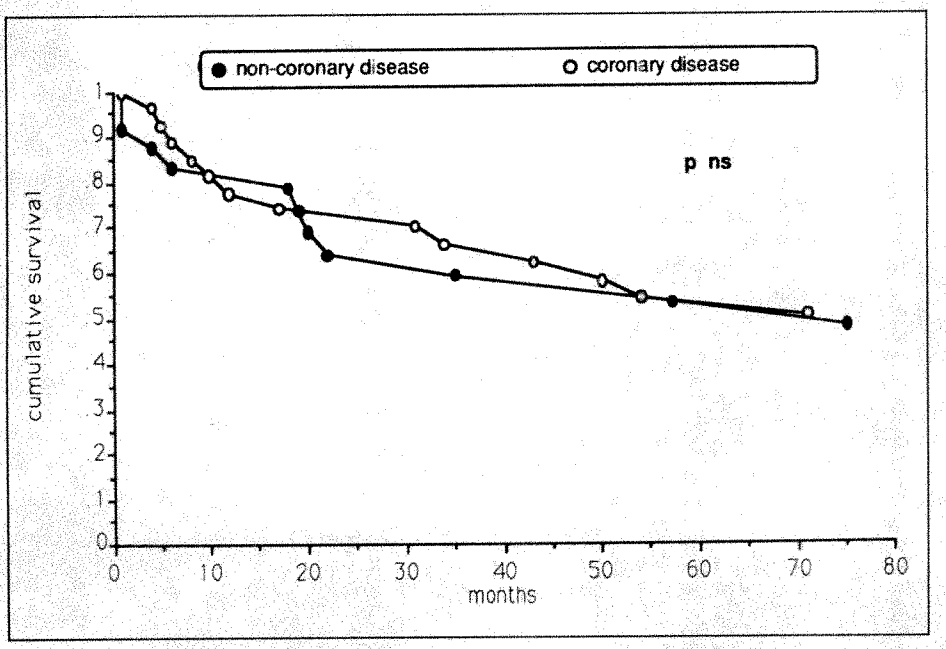


FIGURE 3. Survival curves for patients with clinical congestive heart failure and intact left ventricular systolic function with principal diagnosis of coronary artery disease *(open circles)* versus those without coronary artery disease *(closed circles)*. Fraction of original cohort surviving is displayed on the *y axis*, and time in months on the *x axis*. There is no difference (p = not significant [ns]) in survival between the 2 groups.

mal: 2 of these died, both with sudden pulmonary edema. At 7 years, 6 were alive, although 5 sustained cardiovascular events.

Predictive factors: The number of patients available for analysis of factors which may forecast adverse outcome is small and thus of limited value; yet it is interesting to analyze possible prognostic factors, including underlying diagnosis, clinical presentation and systolic and diastolic function. Survival curves were similar in patients with and without coronary artery disease (Figure 3), as in patients with and without abnormal diastolic function. Cardiovascular mortality was not correlated with any other possible predictive factors at initial presentation, including age, third heart sound, acute pulmonary edema, ejection fraction, peak filling rate or principal diagnosis (all p values >0.10).

DISCUSSION

We have shown in patients identified 7 years ago with CHF and intact systolic performance that a normal LV ejection fraction does not necessarily confer the same favorable prognosis it defines in other clinical circumstances. In most respects the outcome is indistinguishable from that of classic CHF with depressed ejection fraction and substantial early mortality, irrespective of etiology.[1-17]

The poor long-term prognosis of patients with CHF associated with systolic dysfunction, either on an ischemic or idiopathic cardiomyopathic basis, has been well defined. We report no such comparison group, yet published reports provide ample natural history and prognostic data. In these cohorts, 5-year mortality ranges near 50%, as in the Framingham Heart Study and others.[2,3,6,9,11-17] Pump failure or sudden death, presumably caused by ventricular rhythm disturbances, have been implicated in the death of patients with poor contractility.[6,26] CHF with depressed LV function has an unfavorable impact on survival after myocardial infarction.[4] However, patients with pulmonary edema and normal LV ejection fraction in the setting of myocardial infarction have a 1-year outcome comparable to those with depressed ejection fraction.[27]

Mechanisms may exist in our patient group which differ from those that influence prognosis in patients with CHF and LV systolic dysfunction, including intermittent myocardial ischemia, severe impairment of diastolic filling or tachyarrhythmias. The finding that 4 patients died of myocardial infarction suggests a role for transient ischemia in some patients. Acute or recurrent pulmonary edema, or CHF in the setting of another cardiac or systemic illness was the cause of death in 19 patients. Either occult ischemia or primary diastolic abnormalities may have contributed to these mortalities. Instances of sudden death or clinically observed ventricular tachyarrhythmias were few (6%) compared with results in CHF patients with poor LV function, suggesting a lesser role for malignant ventricular rhythms in our patients.

Patients with CHF and normal LV ejection fraction have been described.[18-20] Diastolic filling parameters are abnormal in as many as 38% of these patients.[20] Likely pathophysiologic derangements include impaired cardiac filling based on ischemia, muscle stiffness or delayed relaxation, producing pulmonary congestion, dyspnea and physical and radiographic signs of CHF.[20,28] We have reported a favorable role for calcium antagonists in nonischemic CHF patients with abnormal diastolic filling.[28]

Recently Cohn and Johnson[29] described prognostic findings in patients with CHF and normal LV ejection fraction (≥45%). The results were from the Veterans Administration Vasodilator Heart Failure Trial I (V-HeFT) study examining the use of vasodilators in CHF.[15] The investigators emphasized a subgroup who either had CHF at entry or a history of the same. Previous hypertension was a common factor in this subgroup, a finding also reflected in our data. The V-HeFT study reported a better prognosis for CHF patients with normal systolic function compared to those with CHF and systolic dysfunction (8 vs 19% annual mortality). This finding differs from our results, in which mortality with normal LV function is similar to reported controls with LV systolic dysfunction (24 of 52 [46%] at 7 years in our group, vs 19 of 83 [23%] in 5.7 years in V-HeFT).

Several explanations may account for the disparity between our study and V-HeFT. The mean age was 59.7 ± 6.7 years in the V-HeFT study and was 71 ± 11 years for our patients, who thus had a shorter life expectancy on entry (11.8 years for a 70-year-old man in the USA, vs 18.2 years for a 60-year-old).[30] Could a difference in initial life expectancy alone account for the poor prognosis in our cohort? Reference data suggest not: Our patients survived a mean of 53.7 months (Figure 1) versus 11.8 years for the reference population at large,[30] a major difference.

At entry, our patients were hospitalized with CHF as a major aspect of their presentation, and were referred for evaluation of LV performance because of CHF, an explicit criterion for enrollment. In contrast, the V-HeFT group contained an unspecified fraction who entered based on past CHF. That our patients were more critically ill is suggested by the large number of deaths due to pulmonary edema or recurrent CHF, either primarily, or associated with a systemic stress. In some cases, follow-up showed a decrease in ejection fraction, possibly contributing to later mortality.

Ischemia was systematically excluded in V-HeFT, unlike our study, and may provide an additional explanation for the divergent outcomes. A poor prognosis for patients with normal ejection fraction and ischemic pulmonary edema has been described by Warnowicz et al.[27] Inclusion of ischemia in our patients makes them closer in character to the Warnowicz group than to V-HeFT.[29] By protocol design, half of the patients in the V-HeFT received nitrates and afterload-reducing agents, with possible long-term benefit. With normal LV function, there was a nonsignificant trend toward a decreased annual mortality rate in treated versus placebo patients (5.3 vs 9.0%).[29]

Limitations exist in our study, including the lack of a control group with CHF and abnormal systolic function. Yet numerous series have illustrated an unfavor-

able prognosis in such patients. Though diverse underlying etiologies exist in our group, it is similar to reported groups with CHF and abnormal systolic function, in which several etiologies, ranging from idiopathic dilated cardiomyopathy to ischemic cardiomyopathy, produce a similarly poor prognosis. The hospital-based recruiting of our patients may not permit extrapolation of the findings to outpatients with less CHF. Not all patients had serial radionuclide studies which may have documented declining ejection fractions. That some patients had a decrease in ejection fraction while others did not suggests that a prospective analysis of serial changes in systolic function may be warranted. We cannot address prognosis from the perspective of subsequent drug treatment over 7 years; our purpose was not to describe a prospective therapeutic trial, but simply to define the long-term outcome of this clinical presentation from the time of initial evaluation.

Hospitalized patients with CHF and intact systolic function do not have a favorable long-term outcome. In a separate cohort with abnormal LV diastolic function on a nonischemic basis, short-term improvement is possible using calcium antagonists; whether long-term prognosis can be influenced is unknown.[28] Similarly, in patients with ischemic or restrictive heart disease, survival may be prolonged with specific disease-related therapy; this hypothesis lies outside the scope of the present report. We suggest that hospitalized patients with CHF and intact systolic function do not have a favorable prognosis, and may require careful observation and management.

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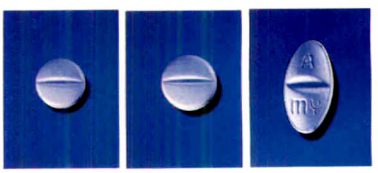
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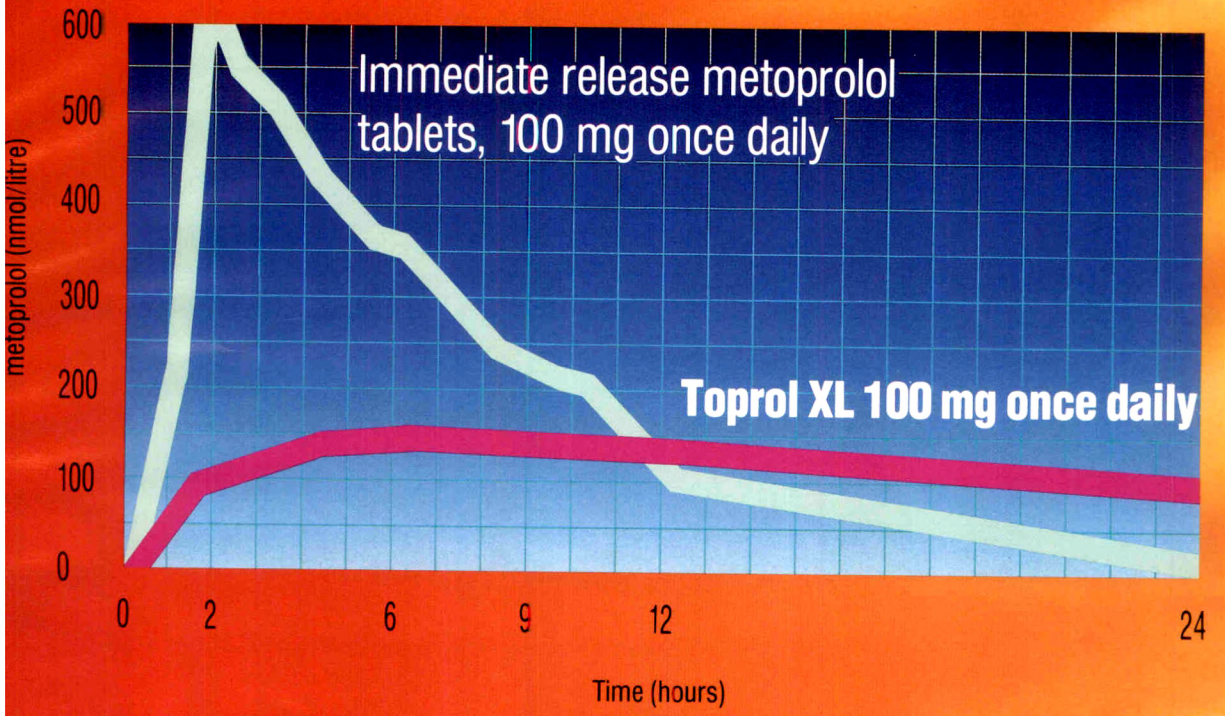
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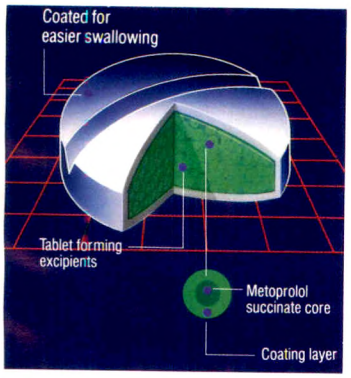
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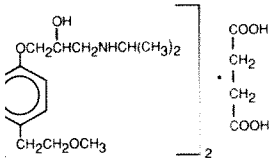
[M] TABLETS

inate)

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olol succinate, is a beta$_1$-selective (cardioselective) adrenoceptor oral administration, available as extended release tablets. Toprol lated to provide a controlled and precictable release of metoprolol inistration. The tablets comprise a multiple unit system containing e in a multitude of controlled release pellets. Each pellet acts as a ery unit and is designed to deliver metoprolol continuously over the e tablets contain 47.5 mg, 95 mg and 190 mg of metoprolol succ- 50, 100 and 200 mg of metoprolol tartrate, USP, respectively. Its (±)1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol t). Its structural formula is:



te is a white crystalline powder with a molecular weight of 652.8. It water; soluble in methanol; sparingly soluble in ethanol; slightly sol- hane and 2-propanol; practically insoluble in ethyl-acetate, acetone, ptane. Inactive ingredients: Silicone dioxide, Cellulose compounds, , Maize starch, Lactose powder, Polyvidone, Magnesium stearate, , Titanium dioxide, Paraffin.

MACOLOGY

beta$_1$-selective (cardioselective) adrenergic receptor blocking agent. fect is not absolute, however, and at higher plasma concentrations, hibits beta$_2$-adrenoreceptors, chiefly located in the bronchial and ire. Metoprolol has no intrinsic sympathomimetic activity, and mem- ctivity is detectable only at plasma concentrations much greater eta-blockade. Animal and human experiments indicate that meto- us rate and decreases AV nodal conduction.

ogy studies have confirmed the beta-blocking activity of metoprolol by (1) reduction in heart rate and cardiac output at rest and upon ction of systolic blood pressure upon exercise, (3) inhibition of iso- tachycardia, and (4) reduction of reflex orthostatic tachycardia.

selectivity of metoprolol has been confirmed by the following: (1) In metoprolol is unable to reverse the beta$_2$-mediated vasodilating rine. This contrasts with the effect of nonselective beta-blockers, reverse the vasodilating effects of epinephrine. (2) In asthmatic ol reduces FEV_1 and FVC significantly less than a non-selective ranolol, at equivalent beta$_1$-receptor blocking doses.

tudies in normal healthy subjects, the same daily doses of Toprol XL ease metoprolol were compared in terms of the extent and duration produced. Both formulations were given in a dose range equivalent immediate release metoprolol per day. In these studies, Toprol XL once a day and immediate release metoprolol was administered a day. A sixth controlled study compared the beta$_1$-blocking effects dose of the two formulations. In each study, beta$_1$-blockade was percent change from baseline, in exercise heart rate following stan- nal exercise tolerance tests at steady state. Toprol XL administered mmediate release metoprolol administered once to four times a day. ble total beta$_1$-blockade over 24 hours (area under the beta$_1$-block- curve) in the dose range 100-400 mg. At a dosage of 50 mg once roduced significantly higher total beta$_1$-blockade over 24 hours than metoprolol. For Toprol XL, the percent reduction in exercise heart stable throughout the entire dosage interval and the level of beta$_1$- ed with increasing doses from 50 to 300 mg daily. The effects at t 24 hours post dosing) were; 14/9, 15/10, 24/14, 27/22 and 27/20% ise heart rate for doses of 50, 100, 200, 300 and 400 mg Toprol XL ctively. In contrast to Toprol XL immediate release metoprolol given 100 mg once a day, produced a significantly larger peak effect on dia, but the effect was not evident at 24 hours. To match the peak to ed with Toprol XL over the dosing range of 200 to 400 mg, a t.i.d. to g regimen was required for immediate release metoprolol.

between plasma metoprolol levels and reduction in exercise heart nt of the pharmaceutical formulation. Using the E_{max} model, the ocking effect has been estimated to produce a 28.3% reduction in te. Beta$_1$-blocking effects in the range of 30–80% of the maximal ding to approximately 8–23% reduction in exercise heart rate) are r at metoprolol plasma concentrations ranging from 30–540 nmol/L. n-effect curve begins reaching a plateau between 200–300 nmol/L, ia levels produce little additional beta$_1$-blocking effect. The relative of metoprolol diminishes and blockade of beta$_2$-adrenoceptors er plasma concentrations.

renergic receptor blockade is useful in the treatment of angina and re are situations in which sympathetic stimulation is vital: in patients naged hearts, adequate ventricular function may depend on sympa- e presence of AV block, beta-blockade may prevent the necessary of sympathetic activity on conduction. Beta$_2$-adrenergic blockade e bronchial constriction by interfering with endogenous adrenergic tivity in patients subject to bronchospasm and may also interfere with hodilators in such patients.

of the antihypertensive effects of beta-blocking agents has not been ver, several possible mechanisms have been proposed: (1) competi- of catecholamines at peripheral (especially cardiac) adrenergic neu- to decreased cardiac output; (2) a central effect leading to reduced ow to the periphery; and (3) suppression of renin activity.

ical studies, an immediate release dosage form of metoprolol has e an effective antihypertensive agent when used alone or as concom- thiazide-type diuretics at dosages of 100–450 mg daily. Toprol XL, 00 to 400 mg once daily, has been shown to possess comparable onventional metoprolol tablets administered two to four times daily. In XL administered at a dose of 50 mg once daily has been shown to sure 24-hours post-dosing in placebo controlled studies. In controlled, nical studies, immediate release metoprolol appeared comparable ensive agent to propranolol, methyldopa, and thiazide-type diuretics, re both in supine and standing positions. Because of variable plasma ith a given dose and lack of a consistent relationship of antihyper- o drug plasma concentration, selection of proper dosage requires .

is

cholamine-induced increases in heart rate, in velocity and extent of action, and in blood pressure, metoprolol reduces the oxygen require- art at any given level of effort, thus making it useful in the long- ent of angina pectoris. However, in patients with heart failure, blockade may increase oxygen requirements by increasing left ength and end-diastolic pressure.

ical trials, an immediate release formulation of metoprolol has been ffective antianginal agent, reducing the number of angina attacks and ise tolerance. The dosage used in these studies ranged from 100 to oprol XL, in dosages of 100 to 400 mg once daily, has been shown to able beta$_1$-blockade as conventional metoprolol tablets administered two y.

tics

ion of metoprolol is rapid and complete. Plasma levels following oral conventional metoprolol tablets, however, approximate 50% of levels enous administration, indicating about 50% first-pass metabolism. es the blood-brain barrier and has been reported in the CSF in a con- of the simultaneous plasma concentration.

chieved are highly variable after oral administration. Only a small frac- (about 12%) is bound to human serum albumin. Elimination is mainly ation in the liver, and the plasma half-life ranges from approximately 3 than 5% of an oral dose of metoprolol is recovered unchanged in the excreted by the kidneys as metabolites that appear to have no clinical llowing intravenous administration of metoprolol, the urinary recovery rug is approximately 10%. The systemic availability and half-life of atients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

In comparison to conventional metoprolol the plasma metoprolol levels following administration of Toprol XL are characterized by lower peaks, longer time to peak and significantly lower peak to trough variation. The peak plasma levels following once daily administration of Toprol XL average one-fourth to one-half the peak plasma levels obtained following a corresponding dose of conventional metoprolol, administered once daily or in divided doses. At steady state the average bioavailability of metoprolol following administration of Toprol XL across the dosage range of 50 to 400 mg once daily, was 77% relative to the corresponding single or divided doses of conventional metoprolol. Nevertheless, over the 24 hour dosing interval, beta$_1$-blockade is comparable and dose-related (see CLINICAL PHARMACOLOGY). The bioavailability of metoprolol shows a dose-related although not directly proportional increase with dose and is not significantly affected by food following Toprol XL administration.

INDICATIONS AND USAGE

Hypertension

Toprol XL tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Toprol XL tablets are indicated in the long-term treatment of angina pectoris.

CONTRAINDICATIONS

Hypertension and Angina

Toprol XL is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta-blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Toprol XL should be administered cautiously. Both digitalis and Toprol XL slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Toprol XL should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Toprol XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1–2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol XL administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol XL therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA-BLOCKERS. Because of its relative beta$_1$-selectivity, however, Toprol XL may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$-selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Toprol XL should be used (see DOSAGE AND ADMINISTRATION).

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Toprol XL like other beta-blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta-blockers.

Diabetes and Hypoglycemia: Toprol XL should be used with caution in diabetic patients if a beta-blocking agent is required. Beta-blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-blockade, which might precipitate a thyroid storm.

PRECAUTIONS

General

Toprol XL should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take Toprol XL regularly and continuously, as directed, preferably with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Toprol XL without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Toprol XL has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Toprol XL.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Toprol XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate the carcinogenic potential of metoprolol tartrate. In 2-year studies in rats at three oral dosage levels of up to 800 mg/kg/day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg/day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed on metoprolol tartrate (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) and metoprolol succinate (a Salmonella/mammalian-microsome mutagenicity test) were negative.

No evidence of impaired fertility due to metoprolol tartrate was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol tartrate has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol tartrate is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantities. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Toprol XL is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children have not been established.

Risk Of Anaphylactic Reactions

While taking beta-blockers, patients with a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient. The following adverse reactions have been reported for metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Toprol XL.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

No overdosage has been reported with Toprol XL and no specific overdosage information was obtained with this drug, with the exception of animal toxicology data. However, since Toprol XL (metoprolol succinate salt) contains the same active moiety, metoprolol, as conventional metoprolol tablets (metoprolol tartrate salt), the recommendations on overdosage for metoprolol conventional tablets are applicable to Toprol XL.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly. On the basis of the pharmacologic actions of metoprolol tartrate, the following general measures should be employed.

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretics should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Toprol XL is an extended release tablet intended for once-a-day administration. When switching from immediate release metoprolol tablet to Toprol XL, the same total daily dose of Toprol XL should be used.

As with immediate release metoprolol, dosages of Toprol XL should be individualized and titration may be needed in some patients.

Hypertension

The usual initial dosage is 50 to 100 mg daily in a single dose, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. Dosages above 400 mg per day have not been studied.

Angina Pectoris

The dosage of Toprol XL should be individualized. The usual initial dosage is 100 mg daily, given in a single dose. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is a pronounced slowing of the heart rate. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1-2 weeks (see WARNINGS).

HOW SUPPLIED

Tablets 50 mg:
Contain 47.5 mg of metoprolol succinate equivalent to 50 mg of metoprolol tartrate, USP
Are white, biconvex, round, film-coated
Engraved $\frac{A}{mo}$ on one side and scored on the other

Bottles of 100 NDC 0186-1090-05

Tablets 100 mg:
Contain 95 mg of metoprolol succinate equivalent to 100 mg of metoprolol tartrate, USP
Are white, biconvex, round, film-coated
Engraved $\frac{A}{ms}$ on one side and scored on the other

Bottles of 100 NDC 0186-1092-05

Tablets 200 mg:
Contain 190 mg of metoprolol succinate equivalent to 200 mg of metoprolol tartrate, USP
Are white, biconvex, oval, film-coated
Engraved $\frac{A}{my}$ and scored on one side

Bottles of 100 NDC 0186-1094-05

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iss. 11/91

FOOTNOTES:

1. Please see full prescribing information above.
2. Sandberg A, Blomqvist I, Jonsson UE, Lundborg P, Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol; a comparison with conventional tablets. Eur J Clin Pharmacol 1988; 33 (Suppl); S9-S14.
3. Data on file at AB Hassle.

Degree of Left Ventricular Hypertrophy in Patients with Hypertrophic Cardiomyopathy and Chronic Atrial Fibrillation

Paolo Spirito, MD, Edward Lakatos, PhD, and Barry J. Maron, MD

It has been generally assumed that most patients with hypertrophic cardiomyopathy (HC) who develop atrial fibrillation (AF) have marked left ventricular (LV) hypertrophy and subaortic obstruction. The morphologic and functional features of this subset of patients with HC have not been systematically investigated. The LV morphology and functional profile of 46 patients with HC and chronic AF were compared with those of 81 control patients with HC and normal sinus rhythm. Contrary to expectations, LV hypertrophy (assessed with 2-dimensional echocardiography) was substantially less marked in the patients with AF than in the control patients, and prevalence of subaortic obstruction was similar in the 2 groups. Maximal LV wall thickness and wall thickness index were lower in patients with AF (18 ± 2 and 56 ± 7 mm, respectively) than in control patients (22 ± 6 and 67 ± 16 mm, respectively; p <0.001). Furthermore, mild LV hypertrophy (maximal LV wall thickness ≤17 mm confined to 1 ventricular segment) was almost twice as frequent in patients with AF (63%) than in control patients (36%; p <0.005). Subaortic obstruction was present in 9 patients with AF (20%) and in 28 control patients (35%; p >0.05). In a subgroup of 22 patients with AF who were followed for 4 to 10 years, 5 patients had marked LV wall thinning (≥5 mm, range 5 to 14). In conclusion, these results demonstrate that most patients with HC and chronic AF have the nonobstructive form of HC, and relatively mild LV hypertrophy. In many of these patients, progressive LV wall thinning is probably responsible for the mild LV hypertrophy.

(Am J Cardiol 1992;69:1217-1222)

From the Echocardiography Laboratory, Cardiology Branch and Biostatistics Research Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. Manuscript received September 5, 1991; revised manuscript received and accepted December 19, 1991.

Address for reprints: Paolo Spirito, MD, Divisione di Cardiologia, Ente Ospedaliero Ospedali Galliera, Via Volta 8, Genoa 16128, Italy.

Atrial fibrillation (AF) is present in a significant minority (approximately 10%) of patients with hypertrophic cardiomyopathy (HC) followed at referral centers.[1-4] In many of these patients, development of AF is associated with symptomatic deterioration and increased risk of systemic embolization.[3-8] Despite the clinical implications of this arrhythmia, the morphologic and functional features of patients with HC and chronic AF have not been investigated systematically. In the present study, in an effort to achieve a better understanding of the characteristics of this subset of patients, we assessed the left ventricular (LV) morphology and functional profile of a large group of patients with HC and chronic AF. These findings were compared with those obtained in a control group of patients with HC and normal sinus rhythm. Our observations provide new insights into the pathophysiology and morphologic evolution of patients with HC who develop chronic AF.

METHODS

Selection and characterization of patients: Forty-six patients with HC who had been in AF for ≥6 months composed the present study cohort. This series represents a consecutive group of patients with HC and chronic AF who were evaluated at the National Heart, Lung, and Blood Institute during a 2-year period and had 2-dimensional echocardiograms of sufficient technical quality for reliable assessment of magnitude and distribution of LV hypertrophy. Two other patients with chronic AF evaluated at the National Heart, Lung, and Blood Institute during this period were not included in the present study group, because they had previously been operated on for relief of subaortic obstruction (ventricular septal myotomy-myectomy). The diagnosis of HC was based on the echocardiographic demonstration of a hypertrophied and nondilated left ventricle in the absence of another cardiac or systemic disease that could produce LV hypertrophy of the magnitude observed.[9]

Patients ranged in age from 19 to 72 years (mean 55). Of the 46 study patients, 27 (59%) were asymptomatic or had only mild symptoms (New York Heart Association functional class I or II), and 19 (41%) had moderate to severe symptoms (functional class III or IV). Presence of LV outflow obstruction under basal conditions was assessed at cardiac catheterization in 30 patients (65%) and estimated from the M-mode echocardiogram on the basis of the magnitude and duration of systolic anterior motion of the mitral valve[10,11] in the other 16 (35%).

Control patients: Morphologic findings in the 46 study patients with chronic AF were compared with those of a consecutive group of 81 patients with HC who were evaluated at the National Heart, Lung, and Blood Institute over the same period of time and met the following criteria: (1) a 2-dimensional echocardiogram of satisfactory technical quality, which permitted reliable assessment of the magnitude and distribution of LV hypertrophy; (2) normal sinus rhythm without documented episodes of AF; and (3) severity of cardiac symptoms similar to that of patients with AF. At the time of the echocardiographic examination, control patients ranged in age from 21 to 74 years (mean 42). Forty-six patients (57%) were asymptomatic or had mild symptoms (New York Heart Association functional class I or II), and the remaining 35 (43%) had moderate to severe symptoms (class III or IV). LV outflow obstruction under basal conditions was assessed at cardiac catheterization in 53 patients (65%) and estimated from the M-mode echocardiogram in the other 28 (35%).

Two-dimensional echocardiography: Two-dimensional echocardiographic images were obtained in the parasternal long- and short-axis views, and apical 2- and 4-chamber views using standard transducer positions.[12] The extent and distribution of LV hypertrophy was assessed at end-diastole using criteria previously described.[13-17] Magnitude of LV hypertrophy was assessed primarily from the parasternal short-axis planes; however, the parasternal long-axis and apical views were also used to integrate the observations obtained from the short-axis views. In the parasternal short-axis plane, the left ventricle was divided in 4 segments that identified the anterior and posterior portions of the ventricular septum, and the lateral and posterior LV free walls. Wall thickness was measured at the levels of both the mitral valve and the papillary muscles in each of the 4 ventricular segments. The segment of the wall with the greatest thickness was considered to represent maximal LV wall thickness.[13,15] Furthermore, an index of the extent of LV hypertrophy was calculated by adding the maximal wall thicknesses measured (at either mitral valve or papillary muscle level) in each of the 4 ventricular segments. These measurements reflect the overall extent of LV hypertrophy, and reliably separate (in quantitative terms) patients with marked and diffuse hypertrophy from those with mild and localized hypertrophy.[13-17] Measurements of both maximal LV wall thickness and wall thickness index were previously shown to have satisfactory reproducibility.[15,16] LV end-diastolic cavity dimension and left atrial size were assessed from the M-mode echocardiogram, as previously described.[18]

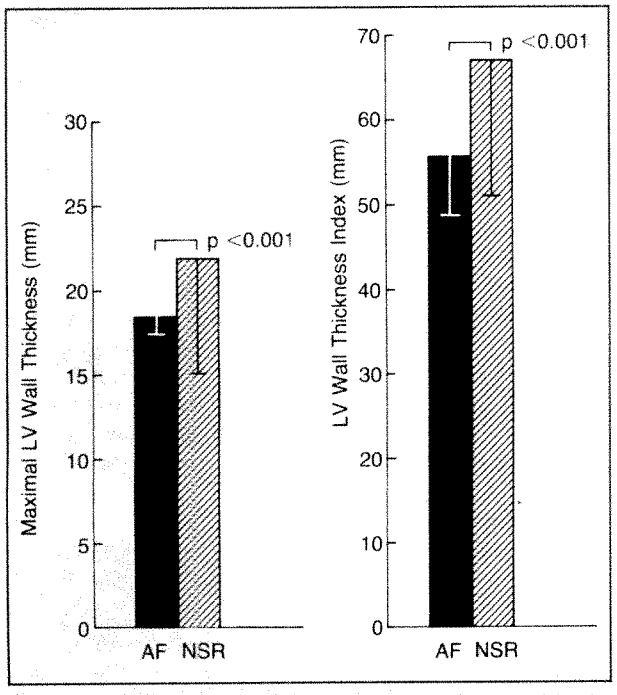


FIGURE 1. Comparison of maximal left ventricular (LV) wall thickness and left ventricular wall thickness index in patients with hypertrophic cardiomyopathy and chronic atrial fibrillation (AF), and in control patients with hypertrophic cardiomyopathy and normal sinus rhythm (NSR).

Echocardiographic follow-up: Serial 2-dimensional echocardiographic measurements of LV wall thickness were obtained in 22 patients with chronic AF who had been followed for ≥4 years (up to 10, mean 7). In each patient, measurements of maximal LV wall thickness, wall thickness index, LV end-diastolic cavity dimension and left atrial size obtained at both the initial and most recent echocardiographic examinations were compared. Serial echocardiographic measurements were obtained without knowledge of the identity of the patient.

Statistical methods: Data were expressed as mean ± SD. Differences between continuous variables were determined using the unpaired or paired Student's *t* test, as appropriate. Differences between proportions were determined using the chi-square or Fisher exact test, as appropriate. Multivariate linear models were used to assess the relation between LV wall thickness and age, as well as that between wall thickness and LV diastolic cavity dimension, left atrial cavity dimension, outflow tract obstruction and functional class after adjusting for age.[19] The regression line relating wall thickness to age in the group with AF was not assumed to have the same slope as that in the control group. A 2-tailed p value ≤0.05 was considered statistically significant.

RESULTS

Left ventricular morphology: The 46 patients with chronic AF and the 81 control patients in normal sinus rhythm were compared with regard to magnitude of LV hypertrophy. Mean values for maximal LV wall thickness were significantly lower in the patients with AF (18 ± 2 mm) than in those in sinus rhythm (22 ± 6 mm; p <0.001) (Figure 1), and ranged from 14 to 24 mm and from 14 to 41 mm, respectively. LV wall thickness index (a measure of the overall extent of LV hypertrophy) was also lower in patients with AF (56 ± 7 mm) than in control patients (67 ± 16 mm; p <0.001) (Figure 1). Furthermore, mild and localized hypertrophy (maximal wall thickness ≤17 mm confined to only 1 LV segment)[20,21] was significantly more frequent in patients with chronic AF (29 of 46, 63%) than in control patients (29 of 81, 36%; p = 0.005). Conversely,

particularly marked and diffuse LV hypertrophy (maximal wall thickness ≥30 mm, or wall thickness ≥25 mm in ≥2 ventricular segments)[20,21] was identified in 13 control patients (16%), but in none of the patients with AF ($p < 0.005$).

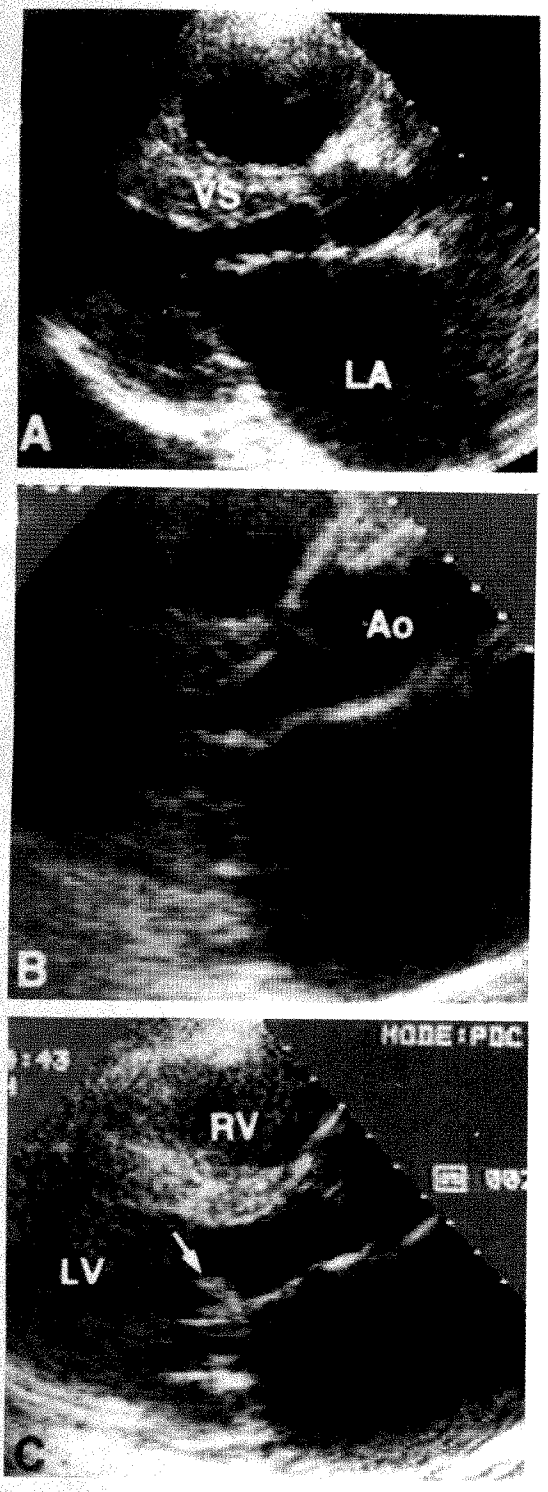


FIGURE 2. Stop-frames of 2-dimensional echocardiograms obtained in parasternal long-axis view during diastole *(A and B)* and at onset of systole *(C)* from 3 patients with hypertrophic cardiomyopathy and chronic atrial fibrillation. There is little morphologic variability among patients, each showing mild hypertrophy of anterior septum and left atrial dilatation. Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle; VS = ventricular septum.

LV morphology was remarkably similar among our study patients with AF, because hypertrophy was relatively mild and mainly involved (or was confined to) the anterior portion of the ventricular septum (Figures 2 and 3). The anterior portion of the septum was the thickest segment in 39 patients (85%) and was the only hypertrophied segment in 23 (50%).

Left atrial size was greater in patients with AF (56 ± 9 mm, range 40 to 85) than in control patients (44 ± 8 mm, range 26 to 65; $p < 0.001$). LV end-diastolic cavity dimension was also greater in patients with AF (47 ± 7 mm, range 38 to 67) than in control patients (43 ± 7 mm, range 31 to 61; $p < 0.005$).

Changes in left ventricular morphology during follow-up: In the subgroup of 22 study patients with AF and echocardiographic follow-up of ≥4 years (up to 10,

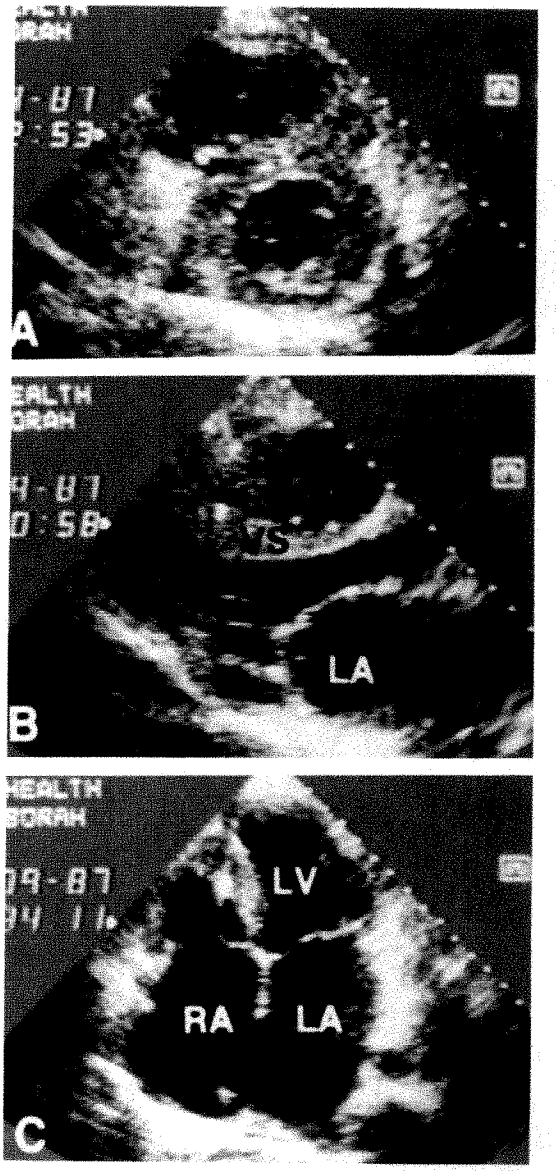


FIGURE 3. Stop-frames of 2-dimensional echocardiogram obtained during diastole in parasternal short- *(A)* and long- *(B)* axis, and apical 4-chamber *(C)* views in a patient with hypertrophic cardiomyopathy and chronic atrial fibrillation. Left ventricular hypertrophy is mild (maximal wall thickness 16 mm), and atria are dilated. RA = right atrium; other abbreviations as in Figure 2.

TABLE I Clinical, Morphologic and Functional Findings in Patients with Hypertrophic Cardiomyopathy and Atrial Fibrillation, and in Patients with Hypertrophic Cardiomyopathy and Normal Sinus Rhythm

	AF	SR	p Value
No. of pts.	46	81	—
Age (yr)	55 ± 13	42 ± 15	<0.001
Men/women	27 (59%)/19 (41%)	46 (57%)/35 (43%)	NS
LV outflow obstruction*	9 (20%)	28 (35%)	NS
Left atrium (mm)	56 ± 9	44 ± 8	<0.001
LV diastolic diameter (mm)	47 ± 7	43 ± 7	<0.005

*Under basal conditions.
AF = atrial fibrillation; LV = left ventricular; NS = not significant; SR = sinus rhythm.

mean 7), maximal LV wall thickness decreased slightly but significantly (19 ± 4 to 17 ± 2 mm; p = 0.02). In 5 patients, the decrease in wall thickness was marked (range 5 to 14 mm). In these patients, maximal LV wall thickness at the initial examination was significantly greater (23 ± 4 mm) than in the remaining 17 (18 ± 3 mm; p = 0.005). LV wall thickness index also decreased significantly during follow-up in this subgroup of 22 patients (60 ± 6 to 55 ± 6 mm; p = 0.01). Furthermore, LV end-diastolic cavity dimension increased significantly (46 ± 4 to 49 ± 6 mm; p <0.01). At the most recent examination, absolute LV cavity dimension remained within normal limits (≤52 mm) in 20 patients (91%) and was increased in only 2 (to 60 and 67 mm, respectively). Left atrial cavity dimension also increased significantly during follow-up (51 ± 8 to 56 ± 9 mm; p <0.001).

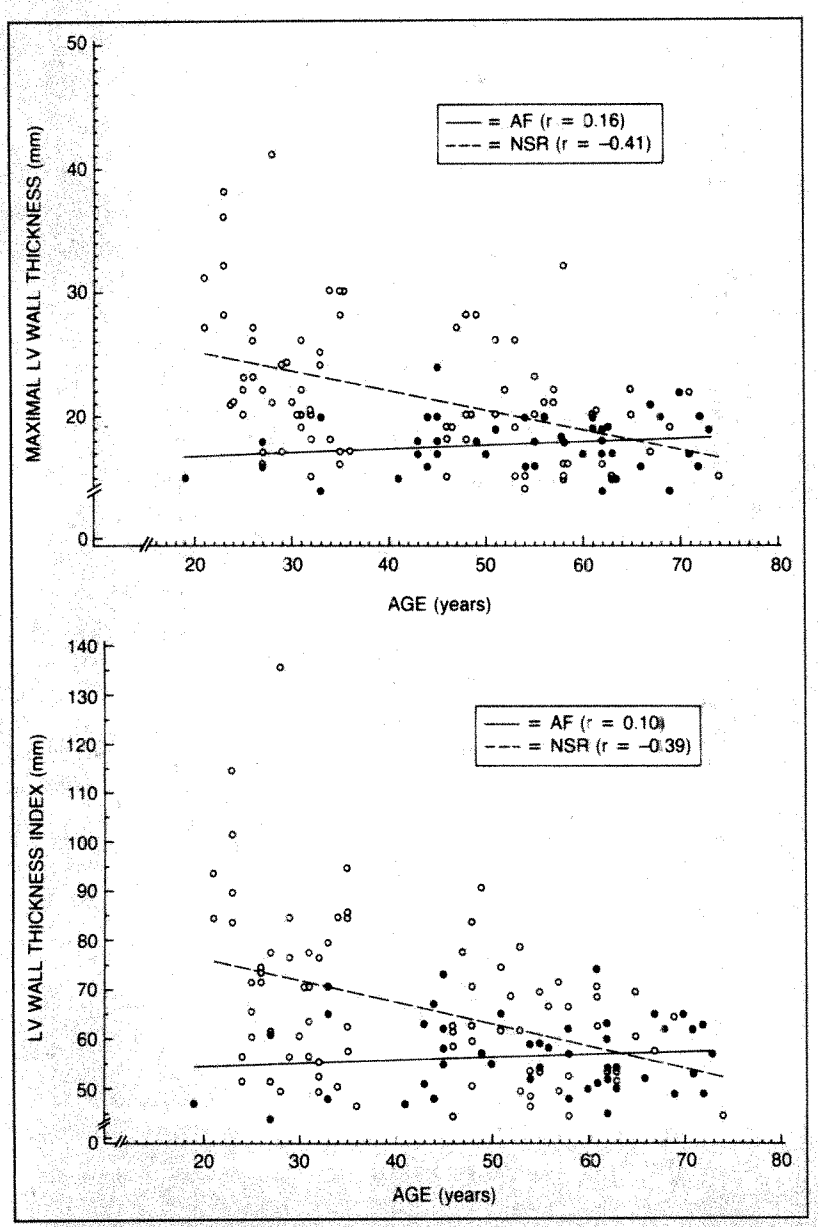


FIGURE 4. Influence of age on maximal left ventricular (LV) wall thickness *(top)* and left ventricular wall thickness index *(bottom)* in 46 patients with hypertrophic cardiomyopathy and chronic atrial fibrillation (AF; *closed symbols and continuous line*), and in 81 control patients with hypertrophic cardiomyopathy and normal sinus rhythm (NSR; *open symbols and broken line*). Age is inversely related to wall thickness in control patients in sinus rhythm, but has no relation to wall thickness in patients with atrial fibrillation.

Clinical and functional findings: Clinical and functional findings in the 46 patients with chronic AF and in the 81 control patients in normal sinus rhythm are listed in Table I. By selection, severity of symptoms in the control patients was similar to that of the patients with AF. Prevalence of outflow obstruction under basal conditions was not significantly different in patients with AF (9 of 46, 20%) from that in control patients in sinus rhythm (28 of 81, 35%; $p > 0.05$).

Patients with AF were significantly older than were control patients (55 ± 13 vs 42 ± 15 years; $p < 0.001$). Furthermore, multiple logistic regression analysis identified age as a predictor of AF independent of LV diastolic cavity dimension, left atrial size, outflow obstruction and functional class ($p < 0.04$). Therefore, we used multivariate linear regression analysis to assess the possible influence of age on the magnitude of LV hypertrophy in the 2 study groups. In the patients with normal sinus rhythm, there was an inverse relation between hypertrophy and age; maximal LV wall thickness had an average decrease of 0.15 mm for each year of age ($p < 0.02$ for the slope being different from 0; $r = -0.41$ for the correlation between wall thickness and age) (Figure 4). The mean difference in maximal wall thickness between the younger (<30 years) and older (>60) control patients was 7 ± 2 mm. In contrast, the patients with chronic AF had no difference in wall thickness with increasing age ($p > 0.8$ for the slope being different from 0; $r = 0.16$ for the correlation between wall thickness and age); the slope of maximal wall thickness against age was virtually 0 (Figure 4). This statistical model also identified a difference in wall thickness between patients with AF and control patients across a wide range of ages, with the difference being greatest in the younger patients; wall thickness was similar between the 2 groups in patients aged >60 years (Figure 4).

DISCUSSION

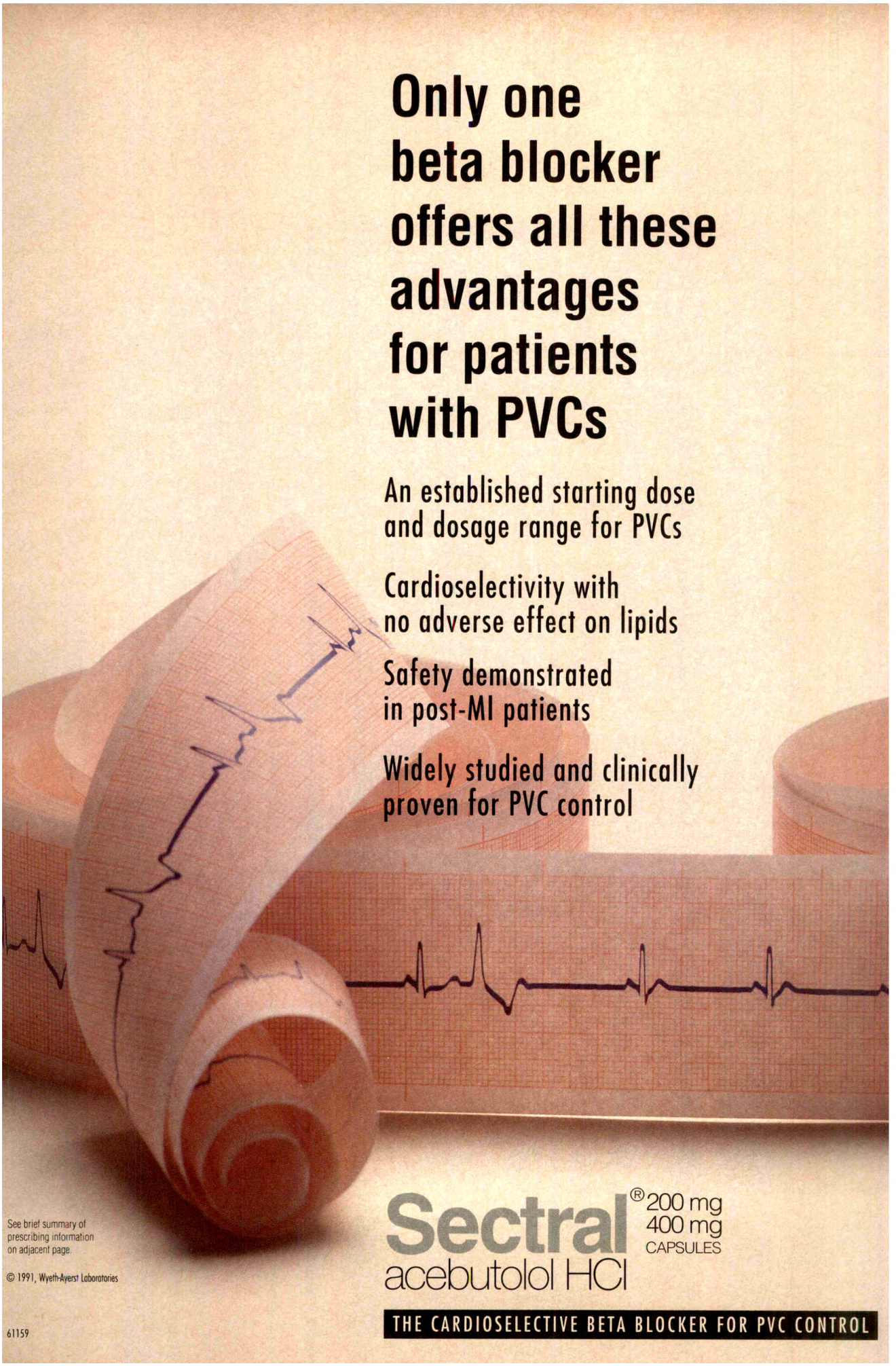
Morphologic and functional features in patients with atrial fibrillation: The results of the present study show that most patients with HC who develop chronic AF have the nonobstructive form of the disease, and mild LV hypertrophy. Approximately 20% of the study patients with AF had subaortic obstruction under basal conditions, a prevalence of obstruction similar to that generally reported for patients with HC.[3,7] Patients with chronic AF had substantially lower maximal LV wall thickness and wall thickness index, as well as a larger LV cavity, than did control patients with HC in normal sinus rhythm. Furthermore, as a group, patients with AF had remarkably similar magnitude and distribution of LV hypertrophy, with mild hypertrophy usually confined to the anterior portion of the septum. This small variability in LV morphology is also well described by the fact that the standard deviations for measurements of wall thickness in the patients with AF were one third of those in control patients in normal sinus rhythm.

Changes in left ventricular morphology during follow-up: The echocardiographic findings during follow-up suggest that the mild and localized LV hypertrophy identified in most patients with HC and chronic AF may result from progressive LV wall thinning. Almost 25% of the study patients followed for ≥4 years had marked wall thinning. Furthermore, patients with this morphologic development had more marked hypertrophy at the initial echocardiographic examination than did other patients with AF. This suggests that some patients with mild LV hypertrophy at the initial examination may have undergone a process of wall thinning before entry into the study. Indeed, we previously showed that progressive LV wall thinning occurs in a significant minority of patients with HC and severe symptoms.[14,15,22] Necropsy and thallium-201 myocardial perfusion studies indicate that this morphologic development probably results from extensive fibrous tissue formation.[23-26] In addition, the inverse relation between age and wall thickness that has been observed in a large population of adult patients with HC suggests that aging may be associated with LV wall thinning in this disease.[20] However, in the present study, multivariate regression analysis showed that age was unrelated to wall thickness in patients with chronic AF, whereas it confirmed our previous finding of an inverse relation between wall thickness and age in control patients in sinus rhythm.[20]

At present, the mechanisms responsible for the strong relation we identified between mild LV hypertrophy and chronic AF in patients with HC remain speculative. Because patients with LV wall thinning usually have severe LV dysfunction and elevated filling pressures,[15] it is possible that the high left atrial pressures lead to atrial dilatation and therefore predispose these patients to the development of AF.

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Use in elderly	**Doses above 800 mg per day should be avoided**

(Brief Summary. See Package Circular for full prescribing information.)

CONTRAINDICATIONS: SECTRAL is contraindicated in: 1) persistently severe bradycardia; 2) second- and third-degree heart block; 3) overt cardiac failure; 4) cardiogenic shock. (See WARNINGS)

WARNINGS: Cardiac Failure: Sympathetic stimulation may be essential for support of circulation in patients with diminished myocardial contractility and inhibition by β-adrenergic receptor blockade may precipitate more severe failure. Although β-blockers should be avoided in overt cardiac failure, SECTRAL can be used cautiously when heart failure is controlled with digitalis and/or diuretics. Digitalis and SECTRAL impair AV conduction. Withdraw SECTRAL if cardiac failure persists.

In Patients Without a History of Cardiac Failure: In patients with aortic or mitral valve disease or compromised left ventricular function, continued depression of the myocardium with β-blockers over time may lead to cardiac failure. Digitalize patients at first signs of failure, and/or give a diuretic and observe closely. Withdraw SECTRAL if cardiac failure persists.

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Abrupt discontinuation of some β-blockers in coronary artery disease patients may exacerbate angina; in some cases, myocardial infarction and death have been reported. Caution such patients against interruption of therapy without a physician's advice. Even in the absence of overt ischemic heart disease, withdraw SECTRAL gradually over a period of about two weeks; observe carefully and advise patients to minimize physical activity during this time. (If desired, patients may be transferred directly to comparable doses of an alternative β-blocker without interruption of β-blocking therapy.) If exacerbation of angina occurs, restart full-dose anti-anginal therapy immediately and hospitalize patient until stabilized.

Peripheral Vascular Disease: β-antagonists reduce cardiac output and can precipitate/aggravate arterial insufficiency in patients with peripheral or mesenteric vascular disease. Exercise caution and observe such patients closely for progression of arterial obstruction.

Bronchospastic Diseases: Patients with Bronchospastic Disease Should, in General, Not Receive a β-Blocker. Because of its relative β_1-selectivity, low doses of SECTRAL may be used cautiously in such patients who do not respond to, or cannot tolerate, alternative treatment. Since β_1-selectivity is not absolute and is dose-dependent, use lowest possible dose of SECTRAL initially, preferably in divided doses. Make bronchodilator, e.g., theophylline, or a β_2-stimulant, available in advance with instructions for use.

Anesthesia and Major Surgery: The necessity/desirability of withdrawing β-blockers prior to major surgery is controversial; the heart's impaired ability to respond to β-adrenergically mediated reflex stimuli may enhance the risk of excessive myocardial depression during general anesthesia. Difficulty in restarting and maintaining the heartbeat also has been reported with beta-blockers. If treatment is continued, take special care when using anesthetics that depress the myocardium; use lowest possible SECTRAL dose. SECTRAL, like other β-blockers, is a competitive inhibitor of β-receptor agonists, so its effects can be reversed by cautious administration of such agents (e.g., dobutamine or isoproterenol). Symptoms of excessive vagal tone (e.g., profound bradycardia, hypotension) may be corrected with atropine.

Diabetes and Hypoglycemia: β-blockers may potentiate insulin-induced hypoglycemia and mask some symptoms such as tachycardia; dizziness and sweating are usually not significantly affected. Warn diabetics of possible masked hypoglycemia.

Thyrotoxicosis: β-adrenergic blockade may mask some clinical signs (tachycardia) of hyperthyroidism. Abrupt withdrawal of SECTRAL may precipitate a thyroid storm in patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Renal or Hepatic Function: While there are no U.S. studies, foreign published experience shows that acebutolol has been used successfully in chronic renal insufficiency. Acebutolol is excreted via the G.I. tract, but the active metabolite, diacetolol, is eliminated mainly by the kidney. A linear relationship exists between renal clearance of diacetolol and creatinine clearance (Cl_{cr}); reduce daily dose of acebutolol by 50% when Cl_{cr} is less than 50 mL/min and by 75% when it is less than 25 mL/min. Use cautiously in patients with impaired hepatic function.

SECTRAL has been used successfully and without problems in elderly patients in U.S. clinical trials without specific dosage adjustment. However, in the elderly, lower maintenance doses may be required because bioavailability of SECTRAL and its metabolite are approximately doubled.

Information for Patients: Warn patients, especially those with evidence of coronary artery disease, against interruption or discontinuation of SECTRAL without physician supervision. Although cardiac failure rarely occurs in properly selected patients, advise patients to consult a physician if signs or symptoms suggestive of impending CHF, or unexplained respiratory symptoms, develop.

Warn patients of possible severe hypertensive reactions from concomitant use of α-adrenergic stimulants, e.g., nasal decongestants used in OTC cold medicines and nasal drops.

Clinical Laboratory Findings: SECTRAL, like other β-blockers has been associated with development of antinuclear antibodies (ANA). In prospective clinical trials, patients receiving SECTRAL had a dose-dependent increase in the development of positive ANA titers. Symptoms related to this laboratory abnormality were infrequent. Symptoms and ANA titers were reversible upon discontinuation of SECTRAL.

Drug Interactions: Catecholamine-depleting drugs may have additive effects when given with β-blockers. Observe patients treated with both agents closely for evidence of marked bradycardia or hypotension which may present as vertigo, syncope/presyncope, or orthostatic changes in blood pressure without compensatory tachycardia. Exaggerated hypertensive responses have been reported from use of β-adrenergic antagonists with α-adrenergic stimulants, including those in OTC cold remedies and vasoconstrictive nasal drops. Nonsteroidal anti-inflammatory drugs may blunt antihypertensive effects of beta-blockers.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies in rats and mice, at doses 15 times the maximum recommended (60 kg) human dose, did not indicate carcinogenic potential for SECTRAL. Diacetolol, the major metabolite in man, was without carcinogenic potential in rats at doses up to 1800 mg/kg/d. SECTRAL and diacetolol also had no mutagenic potential in the Ames Test. No significant impact on reproductive performance or fertility was found in rats following SECTRAL or diacetolol doses of up to 240 or 1000 mg/kg/d, respectively.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B: No teratogenic effects were seen in rat or rabbit reproduction studies utilizing SECTRAL doses that were, respectively, approximately 31.5 and 6.8 times the maximum recommended human dose. At this dose in the rabbit, slight fetal growth retardation was noted; this was considered to be a result of maternal toxicity (evidenced by reduced food intake, lowered rate of body weight gain, mortality). Diacetolol studies (doses up to 450 mg/kg/d in rabbits and up to 1800 mg/kg/d in rats) showed no evidence of fetal harm other than a significant elevation in postimplantation loss with 450 mg/kg/d, a level at which food consumption and body weight gain were reduced in rabbit dams; there was a nonstatistically significant increase in incidence of bilateral cataract in rat fetuses from dams treated with 1800 mg/kg/d. There are no adequate and well-controlled trials in pregnant women; SECTRAL should be used during pregnancy only if potential benefit justifies risk to the fetus.

Nonteratogenic Effects: Human studies indicate that acebutolol and diacetolol cross the placenta. Neonates of mothers who received acebutolol during pregnancy have reduced birth weight, decreased blood pressure, and decreased heart rate.

Labor and Delivery: Effect on labor and delivery in pregnant women is unknown. Animal studies have shown no effect of SECTRAL on the usual course of labor and delivery.

Nursing Mothers: Acebutolol and diacetolol appear in breast milk (milk: plasma ratio of 7.1 and 12.2, respectively). Use in nursing mothers is not recommended.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: SECTRAL is well tolerated in properly selected patients. Most adverse effects have been mild, not required therapy discontinuation, and tended to decrease as treatment duration increases.

The incidence of treatment-related side effects (volunteered and elicited) derived from U.S. controlled clinical trials in patients with hypertension, angina and arrhythmia follows. Numbers represent percentage incidence for SECTRAL (N = 1002) versus placebo (N=314), respectively.

Cardiovascular: Chest pain 2%, 1%; Edema 2%, 1%. *CNS:* Depression 2%,1%; Dizziness 6%, 2%; Fatigue 11%, 4%; Headache 6%, 4%; Insomnia 3%, 1%; Abnormal dreams 2%, 1%. *Dermatologic:* Rash 2%, 1%. *Gastrointestinal:* Constipation 4%, 0%; Diarrhea 4%, 1%; Dyspepsia 4%, 1%; Flatulence 3%, 1%; Nausea 4%, 0%. *Genitourinary:* Micturition (frequency) 3%, <1%. *Musculoskeletal:* Arthralgia 2%, 2%; Myalgia 2%, 0%. *Respiratory:* Cough 1%, 0%; Dyspnea 4%, 2%; Rhinitis 2%, <1%. *Special Senses:* Abnormal Vision 2%, 0%.

The following selected (potentially important) side effects were seen in up to 2% of SECTRAL patients: *Cardiovascular:* hypotension, bradycardia, heart failure. *CNS:* anxiety hyper/hypoesthesia, impotence. *Skin:* pruritus. *Gastrointestinal:* vomiting, abdominal pain. *Genitourinary:* dysuria, nocturia. *Liver and Biliary:* small number of reported cases of liver abnormalities (increased SGOT, SGPT, LDH). In some cases, increased bilirubin or alkaline phosphatase, fever, malaise, dark urine, anorexia, nausea, headache, and/or other symptoms have been reported. In some cases, symptoms and signs were confirmed by rechallenge. Abnormalities were reversible upon drug cessation. *Musculoskeletal:* back and joint pain. *Respiratory:* pharyngitis, wheezing. *Special Senses:* conjunctivitis, dry eye, eye pain. *Autoimmune:* extremely rare reports of systemic lupus erythematosis.

Incidence of drug-related adverse effects (volunteered and solicited) based on SECTRAL dose is shown below. (Data from 266 hypertensive patients treated for 3 months on a constant dose.)

Body System	400 mg/day (N = 132)	800 mg/day (N = 63)	1200 mg/day (N = 71)
Cardiovascular	5%	2%	1%
Gastrointestinal	3%	3%	7%
Musculoskeletal	2%	3%	4%
Central Nervous System	9%	13%	17%
Respiratory	1%	5%	6%
Skin	1%	2%	1%
Special Senses	2%	2%	6%
Genitourinary	2%	3%	1%

Potential Adverse Effects: Certain adverse effects not listed above have been reported with other β-blocking agents and should be considered as potential adverse effects of SECTRAL.

CNS: Reversible mental depression progressing to catatonia, an acute syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS). *Allergic:* Erythematous rash, fever with aching and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, nonthrombocytopenic and thrombocytopenic purpura.

Gastrointestinal: Mesenteric arterial thrombosis, ischemic colitis.

Miscellaneous: Reversible alopecia, Peyronie's disease. The oculomucocutaneous syndrome associated with practolol has not been reported with SECTRAL.

Keep at room temperature, Approximately 25°C (77°F).

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Measurement of Right Ventricular Mass in Normal and Dilated Cardiomyopathic Ventricles Using Cine Magnetic Resonance Imaging

Neil E. Doherty III, MD, Naoya Fujita, MD, Gary R. Caputo, MD, and Charles B. Higgins, MD

The accurate quantification of right ventricular (RV) mass has eluded conventional imaging modalities. Accordingly, cine magnetic resonance imaging was used for quantification of RV as well as left ventricular (LV) mass in 10 normal subjects and in 10 patients with dilated cardiomyopathy with an LV ejection fraction <0.40. Hearts were imaged with 10 mm thick short-axis slices from apex to base with a short echo delay time of 5 ms. Each slice was partitioned into 3 sections: RV free wall, ventricular septum and LV free wall, for calculation of end-diastolic and end-systolic mass and LV:RV free wall ratio. RV end-diastolic mass in normal subjects was 45 ± 8 g, which was similar to the values determined in previously published postmortem studies, mean 46 g (range 23 to 68). The value determined in patients with dilated cardiomyopathy was higher (50 ± 11 g), but this difference was not significant. LV:RV free wall ratio in cardiomyopathy (3.6 ± 1.0) was greater than in normal subjects (2.4 ± 0.3), because of the greater LV free wall mass in dilated cardiomyopathy, where LV free wall end-diastolic mass was 173 ± 40 g vs 107.1 ± 19.9 g in normal subjects (p <0.05). RV mass measurements had 6.4 ± 3.6% interobserver and 7.3 ± 6.1% intraobserver variability. There were no significant differences between end-diastolic and end-systolic mass measurements. Thus, cine magnetic resonance imaging can reproducibly calculate RV mass. The values in normal subjects correspond to previously reported postmortem values for a population without heart disease.

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Recently, it has been shown that in vitro right ventricular (RV) mass can be accurately measured postmortem with spin-echo magnetic resonance imaging (MRI).[1] Further interest in the measurement of RV mass was stimulated by the in vivo measurement of RV mass by ultrafast computed tomography.[2] Because MRI also is based on tomographic imaging, but is more available than ultrafast computed tomography, the current study sought to assess the capability of cine MRI to measure RV mass in normal subjects and in patients with dilated cardiomyopathy. Values calculated from cine MRI were compared with normal values established by postmortem studies. RV mass measurements in dilated cardiomyopathy have not been previously reported.

METHODS

Study subjects: The study group included 10 normal volunteers, aged 25 to 56 years, and 10 patients with dilated cardiomyopathy, aged 34 to 73 years. The diagnosis of dilated cardiomyopathy was based on clinical information and 2-dimensional echocardiographic or scintigraphic measured ejection fraction <0.40. All patients were considered to be in New York Heart Association Class II (n = 3) or III (n = 7). No patients had significant valvular regurgitation. The cine MRI studies were approved by the Human Research Committee at the University of California, San Francisco, and all subjects gave informed consent.

Imaging technique: Cine MRI was performed with a commercially available 1.5T superconducting magnet (General Electric, Milwaukee, Wisconsin). Cine MRI was recorded in the short-axis plane[3] with gradient refocused echoes with a short echo delay time of 5 ms, TR of 32 ms, and flip angle 30° in 10 mm slices of the heart from apex to base. No gap between slices was accomplished by interdigitating slices on alternating acquisitions. Two slices were acquired on each acquisition. To encompass the entire right ventricle, 8 to 12 tomographic levels were acquired for each study.

Image analysis: Images were analyzed independently by 2 observers off-line on a Signa console (General Electric, Milwaukee, Wisconsin). Standardized width and level settings were used for image display to trace epicardial and endocardial borders for each slice.[4] To accurately define edges, signal intensity region-of-interest measurements were obtained on each image for RV free wall, chest wall, RV inferior wall, liver, RV cavity, interventricular septum, LV free wall, LV cavity and lung. Levels were set at myocardial signal intensity ± 0.15 × signal intensity of the adjacent surface. Widths

TABLE I Right Ventricular Mass and Free Wall Thickness in Normal Subjects and in Patients with Dilated Cardiomyopathic Ventricles

	Normal	Dilated Cardiomyopathy
RV free wall end-diastolic mass	44.6 ± 7.8 g	49.7 ± 11.2 g
RV free wall end-systolic mass	44.3 ± 7.0 g	49.3 ± 11.8 g
Interventricular septum end-diastolic mass	53.8 ± 12.2 g	76.4 ± 12.8 g*
Interventricular septum end-systolic mass	52.2 ± 11.1 g	73.6 ± 10.7 g*
LV free wall end-diastolic mass	107.1 ± 19.9 g	173.2 ± 40.0 g†
LV free wall end-systolic mass	105.4 ± 19.0 g	175.3 ± 39.3 g†
LV/RV end-diastolic mass	2.4 ± 0.3	3.6 ± 1.0*
LV/RV end-systolic mass	2.4 ± 0.2	3.5 ± 0.9*
RV free wall end-diastolic thickness	3.8 ± 0.3 mm	4.5 ± 0.6 mm*
RV end-diastolic volume	117 ± 19 ml	128 ± 17 ml

*$p < 0.01$; †$p < 0.05$.
Values are mean ± standard deviation.
LV = left ventricular; RV = right ventricular.

TABLE II Interobserver Variability of Mass Measurements in Normal Subjects and in Patients with Dilated Cardiomyopathic Hearts

	Normal (%)	Dilated Cardiomyopathy (%)
RV free wall end-diastolic mass	4.1 ± 2.7	6.7 ± 4.6
RV free wall end-systolic mass	5.0 ± 3.2	6.4 ± 3.6
Ventricular septum end-diastolic mass	8.1 ± 5.4	8.3 ± 6.1
Ventricular septum end-systolic mass	8.0 ± 6.1	7.4 ± 7.1
LV free wall end-diastolic mass	5.3 ± 4.0	6.4 ± 5.1
LV free wall end-systolic mass	4.9 ± 4.5	5.4 ± 4.1
LV:RV free wall end-diastolic mass	5.2 ± 5.0	8.5 ± 7.9
LV:RV free wall end-systolic mass	5.5 ± 4.9	9.6 ± 6.7

Values are mean ± standard deviation.
LV = left ventricular; RV = right ventricular.

were set as the difference in signal intensity between adjacent surfaces. Images were analyzed independently by 2 observers and repeated ≥4 weeks later by the first observer. Myocardial volumes were calculated using Simpson's rule. Mass was calculated by multiplying this value by the density of heart muscle, 1.055 g/ml.

Each slice was partitioned into 3 sections: RV free wall, interventricular septum, and LV free wall for calculations of end-diastolic and end-systolic mass. Figure 1 illustrates the partitioning of a typical midventricular slice. The method for partitioning the ventricular myocardium is shown in Figure 2. The RV free wall is partitioned by a line continuing from the RV cavity–interventricular septal junction, continuing through to the epicardial RV free wall–interventricular junction point. Straight lines are drawn from the superior epicardial–septal junction and inferior epicardial–septal junction to the center of the LV cavity in order to partition the interventricular septum and LV free wall. Masses were summed for each segment from apex to base.

Figure 1 is photographed at level, width and window settings appropriate for the anterior free wall, where the cross hair is placed. The lower free wall is not fully visualized in Figure 1 because it has a lower signal intensity,

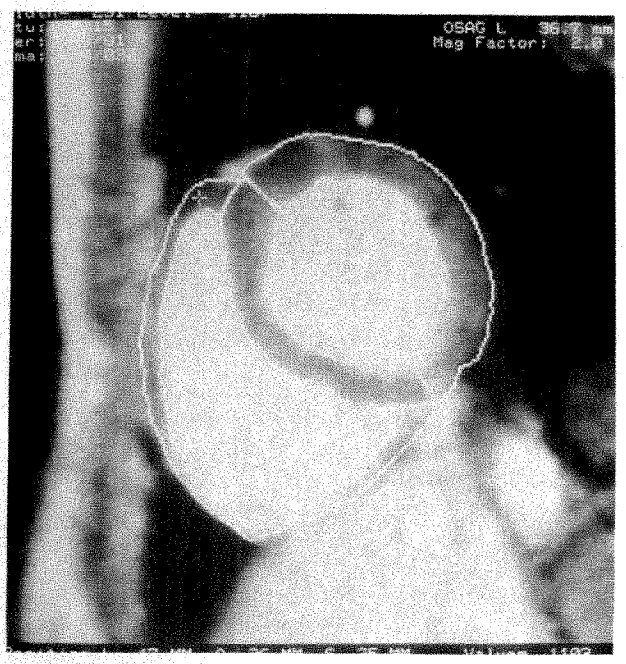


FIGURE 1. Midventricular slice of normal heart with endocardial and epicardial edges traced and heart partitioned into right ventricular free wall, interventricular septum and left ventricular free wall.

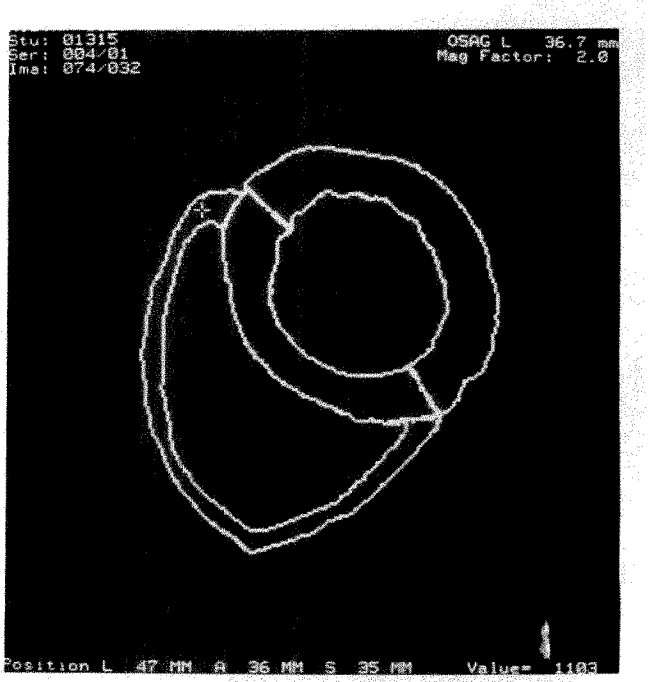


FIGURE 2. Midventricular slice of normal heart with endocardial and epicardial edges traced in silhouette to depict partitioning of heart into right ventricular free wall, interventricular septum and left ventricular free wall.

and was therefore measured at a lower window level but without having to extrapolate from adjacent portions of the RV free wall.

Statistics: Values are expressed as mean ± standard deviation. Differences between observers and observations in mass and LV:RV free wall ratio were compared with a Student's 2-tailed *t* test with differences considered significant at $p < 0.05$. The interobserver and intraobserver percent variability for each mass measurement was determined as the quotient of the absolute value of the difference between the 2 measurements and the mean of the 2 measurements.[5,6] Linear regression analysis was performed to calculate interobserver and intraobserver reproducibility with standard error of the estimate (SEE) for each mass measurement and LV/RV mass ratio.

RESULTS

Table I lists mean values for RV free wall, interventricular septum and LV free wall end-diastolic and end-

TABLE III Intraobserver Variability of Mass Measurements in Normal Subjects and in Patients with Dilated Cardiomyopathic Hearts

	Normal (%)	Dilated Cardiomyopathy (%)
RV free wall end-diastolic mass	3.8 ± 1.9	7.3 ± 6.1
RV free wall end-systolic mass	4.8 ± 4.3	5.4 ± 6.5
Ventricular septum end-diastolic mass	7.6 ± 6.8	7.6 ± 5.7
Ventricular septum end-systolic mass	5.1 ± 4.3	5.6 ± 3.6
LV free wall end-diastolic mass	3.3 ± 2.2	5.1 ± 3.9
LV free wall end-systolic mass	3.7 ± 2.7	4.9 ± 3.6
LV:RV free wall end-diastolic mass	4.6 ± 3.8	7.3 ± 6.9
LV:RV free wall end-systolic mass	4.7 ± 5.4	7.6 ± 4.7

Values are mean ± standard deviation.
LV = left ventricular; RV = right ventricular.

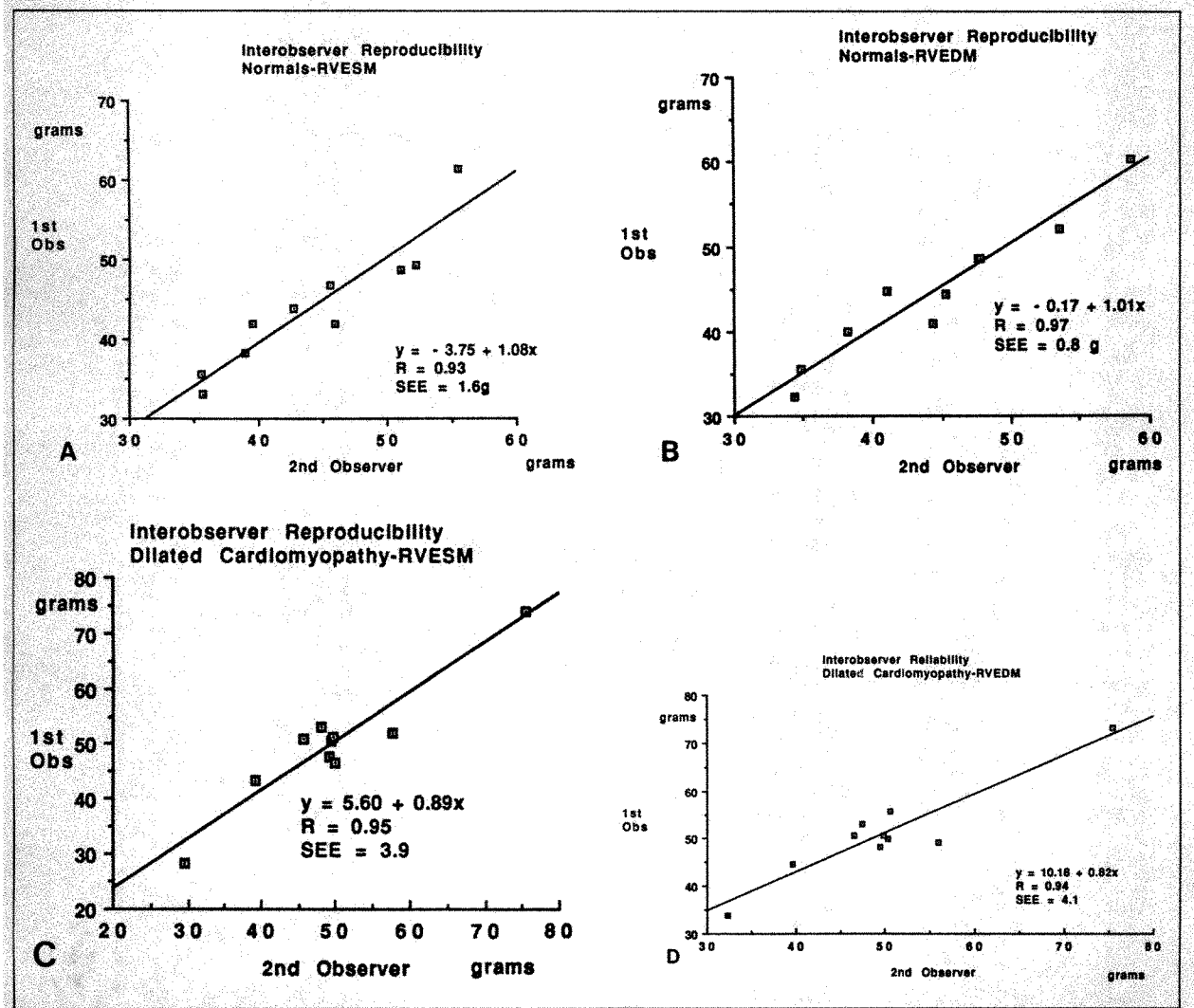


FIGURE 3. Plots show interobserver reproducibilities for right ventricular end-systolic (RVESM) and end-diastolic mass (RVEDM) for normal subjects *(A, B)* and patients with dilated cardiomyopathy *(C, D)*. Correlation coefficients (R) were >0.93 for all measurements.

systolic mass measurements. Table I also lists mean values for RV free wall thickness at end-diastole. There were no significant differences in mass measurements at end-diastole compared with end-systole. Mean value for RV free wall measurements at end-diastole in normal volunteers was 45 ± 8 g. LV:RV free wall mass ratio at end-diastole was 2.4 ± 0.3. RV free wall thickness was 3.8 ± 0.3 mm.

In dilated cardiomyopathy, RV free wall mass at end-diastole was slightly greater (50 ± 11 g), but this was not significantly different than in normal hearts. RV free wall thickness in dilated cardiomyopathy was 4.5 ± 0.6 mm, which was significantly greater ($p < 0.01$) than in normal subjects.

End-diastolic LV:RV free wall ratio in dilated cardiomyopathic hearts was 3.6 ± 1.0, which was higher than in normal hearts ($p < 0.01$) because of higher LV mass ($p < 0.05$). LV free wall mass at end-diastole in dilated cardiomyopathic ventricles was 173 ± 40 g compared with 107 ± 20 g in normal hearts ($p < 0.05$). Interventricular septal mass was greater in dilated cardiomyopathic hearts than in normal hearts. Interventricular septum end-diastolic mass in dilated cardiomyopathy was 76 ± 13 g compared with 54 ± 12 g in normal hearts ($p < 0.01$).

The variability of measurements in the normal and dilated cardiomyopathic hearts is presented in Tables II and III. RV mass measurements had 6 ± 4% interobserver variability and 7 ± 6% intraobserver variability. There was a trend suggesting more variability in dilated cardiomyopathic hearts than in normal hearts but the differences were not significant. Variability of RV mass measurements was not significantly different from that for LV mass measurements.

Figures 3 and 4 show linear regressions, with correlation coefficients and SEE, for interobserver (Figure 3) and intraobserver (Figure 4) reproducibility of RV end-diastolic and end-systolic mass measurements in normal and dilated cardiomyopathic hearts. Correlation coefficients range from 0.93 to 0.99 and SEE ranges from 0.8 to 4.5 g, confirming that the technique is highly reproducible.

DISCUSSION

This study is the first report of in vivo measurement of RV mass using MRI. The study demonstrates that

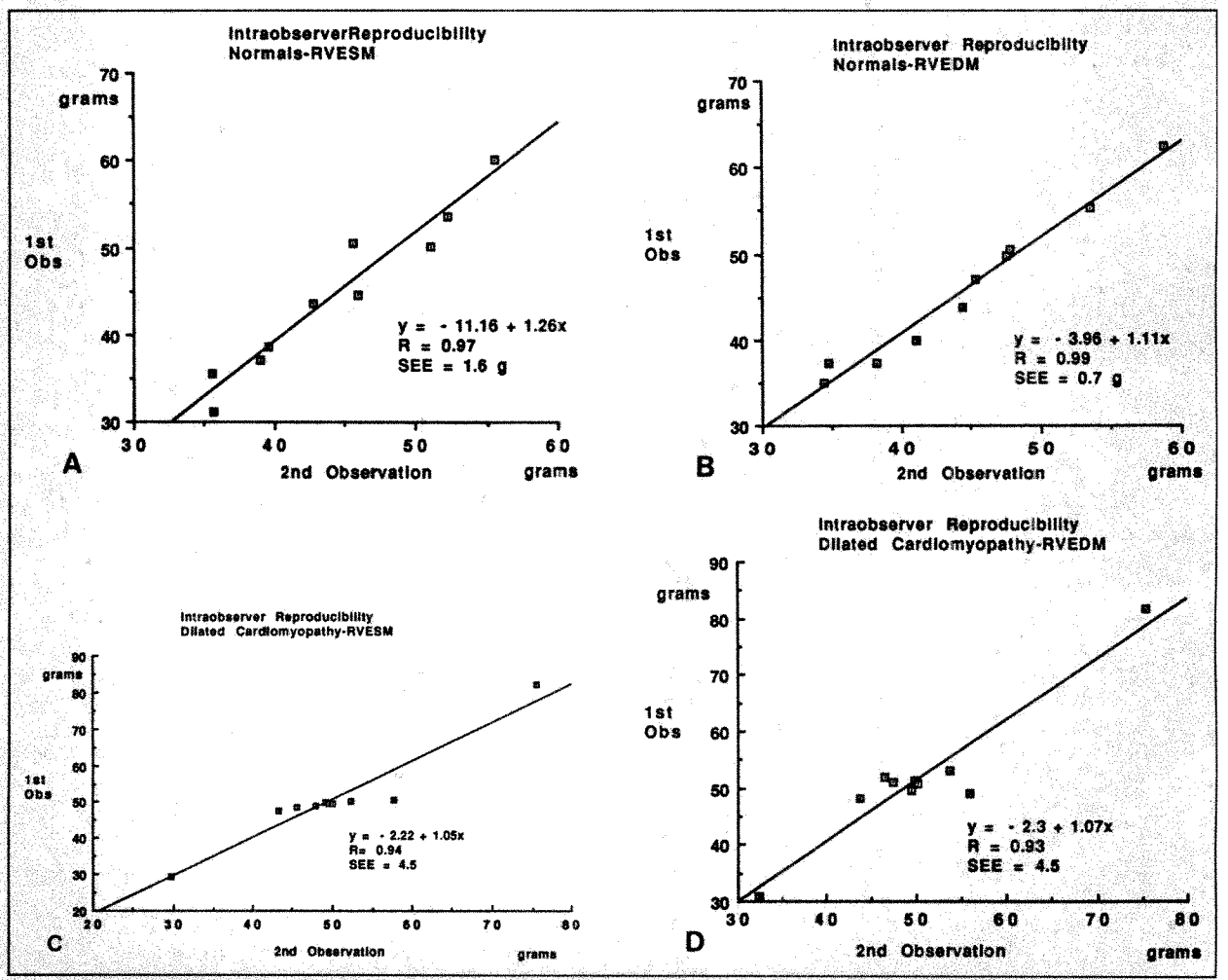


FIGURE 4. Plots show intraobserver reproducibilities for right ventricular end-systolic (RVESM) and end-diastolic mass (RVEDM) for normal subjects *(A, B)* and patients with dilated cardiomyopathy *(C, D)*. Correlation coefficients (R) were >0.93 for all measurements.

cine MRI with short echo delay times can be used to measure RV free wall mass with a high degree of reproducibility. Measurements of mass by cine MRI agree with necropsy measurements of RV free wall mass and LV:RV free wall ratios.[7] Mean value for RV free wall measurements in normal volunteers at end-diastole was 45 ± 8 g. Mean value for LV:RV free wall mass ratio was 2.4 ± 0.3. These values are comparable to necropsy measurements of RV free wall mass (mean 46 g, range 23–68) and LV:RV free wall ratio 1.9 in subjects aged <76 years and without evidence of heart disease.[7] In contrast, ultrafast computed tomography reported slightly higher values for mean RV free wall mass, 55 ± 3 g in 7 young healthy male volunteers.[2]

Cine MRI showed slightly higher values for RV mass in dilated compared with normal ventricles but these differences were not significant. However, RV free wall thickness was significantly greater in dilated cardiomyopathic hearts than in hearts of normal subjects. LV:RV free wall ratio in dilated cardiomyopathic hearts at end-diastole was significantly higher than in normal hearts due to a higher LV mass. The increase in LV mass in dilated cardiomyopathy has been shown previously with MRI.[6] Previous studies have shown a wide variability of RV mass and RV free wall thickness in patients with left-sided cardiac disease.[7,8] An echocardiographic evaluation of the RV wall thickness with proximate confirmation by postmortem measurements indicated both increased and normal wall thickness in patients with LV cardiomyopathy.[8] The slight but not significant increase in RV free wall mass in patients with class II and III functional status in the current study is consistent with this variable occurrence of RV hypertrophy in patients with dilated cardiomyopathy.

The reproducibility data of the current study suggest that cine MRI is a highly reproducible technique for measurement of RV mass, with interobserver variabilities of 4 ± 3 to 7 ± 5% and intraobserver variabilities of 4 ± 2 to 7 ± 6%. Furthermore, the variability of RV mass measurements was not significantly different from the variability of LV mass measurements, which were in the range of interobserver variability reported by Semelka et al[5,6] for normal and dilated cardiomyopathy.

The most important technical refinement to enable measurement of RV mass by cine MRI was shortening of the echo delay time to 5 ms. Initial attempts at quantification of RV mass using an echo delay time of 17 ms gave unsatisfactory edge discrimination and excess slow-flow artifact for accurate delineation of RV borders. Earlier reports using spin-echo images with echo delay time of 34 ms measured RV free wall thickness but did not report RV free wall mass and were only able to give a clear image of 68% of the RV free wall.[9]

There were a few areas of the heart where measurement of RV mass by cine MRI was difficult. The RV apex usually, but not always, extended to the level of the LV apex. When the 2 ventricles shared the apex and no cavity was present, assignment of mass to right or left ventricle was inferred by comparison to adjacent levels. Other areas of difficulty were identifying the borders of the pulmonic and tricuspid valves. The valves were not usually seen, although their position could be ascertained by differences in flow between right atrium, right ventricle and pulmonary artery. However, this information itself was not usually necessary to determine where the RV muscle stopped. The inferior border of the right ventricle could sometimes be clearly distinguished from the liver, but usually the difference in signal characteristics between inferior RV myocardium and liver was small and it was then necessary to extrapolate from RV free wall to the inferior wall adjacent to the septum, which was well delineated from other structures. The conus section of the right ventricle was readily defined and this portion was included in the measurements.

The accuracy of nontomographic techniques for the estimation of RV mass is limited. The electrocardiogram is very insensitive for RV hypertrophy and is a poor predictor of absolute RV mass.[10,11] Surface echocardiography is limited by poor resolution due to inadequate acoustical windows and therefore gives poor estimates of RV mass.[12–15] Radionuclide ventriculography cannot assess RV wall thickness or mass.[16–18] Biplane angiography cannot determine RV mass or wall thickness due to overlap with LV mass.[19,20]

RV mass measurements may be useful for monitoring the effects of therapy in patients with right-sided cardiac diseases[21] or pulmonary hypertension.[22] It has also been speculated that RV mass may be an important prognostic measurement in some diseases,[2] particularly chronic obstructive pulmonary disease. A full assessment of RV function, including volumes, ejection fraction and mass, is now possible with either ultrafast computed tomography[23] or MRI.[24,25]

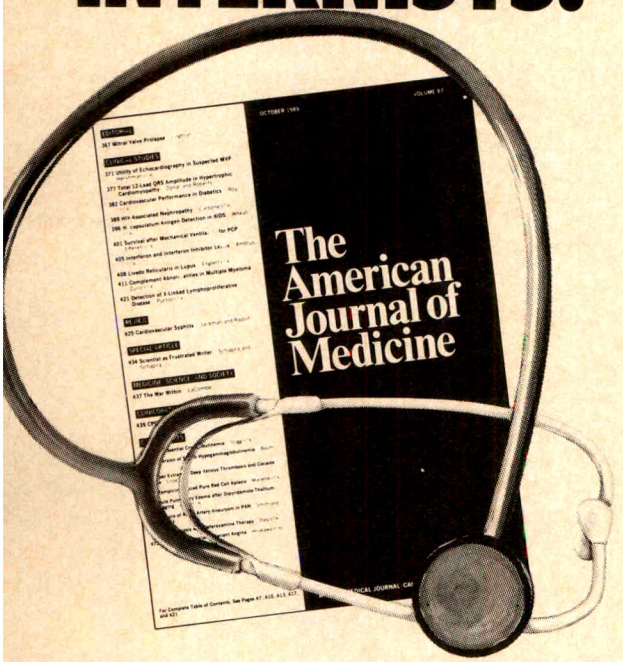
The response of the right ventricle to diseases affecting the left ventricle can be studied with these tomographic techniques. The current study showed slightly greater RV mass in dilated cardiomyopathy. The measurement of RV mass in hypertensive LV hypertrophy and hypertrophic cardiomyopathy should be studied to see how these conditions influence the right ventricle.

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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Hypertension
Lopressor tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.
Angina Pectoris
Lopressor is indicated in the long-term treatment of angina pectoris.
Myocardial Infarction
Lopressor ampuls and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous Lopressor can be initiated as soon as the patient's clinical condition allows (see **DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS,** and **WARNINGS**). Alternatively, treatment can begin within 3 to 10 days of the acute event (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS
Hypertension and Angina
Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **WARNINGS**).
Myocardial Infarction
Lopressor is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see **WARNINGS**).

WARNINGS
Hypertension and Angina
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.
In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**
Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.
Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.
Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.
Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.
During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.
AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.
If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.
Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).
Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS
General
Lopressor should be used with caution in patients with impaired hepatic function.
Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.
Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.
Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.
Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.
Risk of Anaphylactic Reaction. While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.
All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.
No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.
Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Hypertension and Angina
Most adverse effects have been mild and transient.
Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.
Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)
Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).
Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.
Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.
Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.
There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.
The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.
Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.
Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.
Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.
Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.
Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.
Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.
Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.
Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).
Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.
Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE
Acute Toxicity
Several cases of overdosage have been reported, some leading to death.
Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.
Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.
Treatment
There is no specific antidote.
In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).
On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:
Elimination of the Drug: Gastric lavage should be performed.
Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.
Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.
Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.
Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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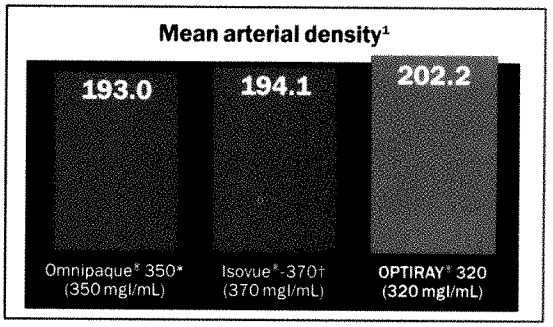


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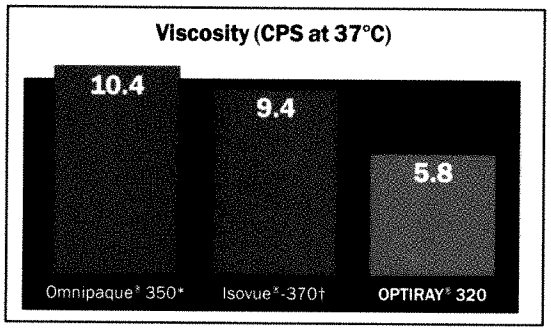
Great cardiac visualization with the safety of lower iodine...

A recent clinical study showed that OPTIRAY® 320 (ioversol injection 68%) provides equivalent image density when compared with contrast agents of higher iodine concentration.[1]

So OPTIRAY® 320 provides a means for reducing the amount of iodine administered with no reduction in overall image quality. And a lower iodine dose may reduce the likelihood of renal dysfunction.[2]

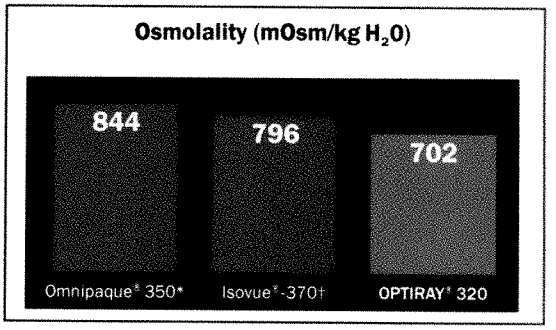


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The low viscosity and greater flow rate of OPTIRAY® 320 mean easier hand injections and images equivalent to contrast agents with a higher iodine concentration.[1]

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OPTIRAY® 320 has the lowest osmolality of these nonionic contrast media.

Sometimes all you need is a little less, to get more.

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

References:

1. Kern MJ, Roth RA, Aguirre FV, Beauman G, Vogel R. Effect of viscosity and iodine concentration of nonionic radiographic contrast media on coronary arteriography in pa *Am Heart J.* 1992; 123:160-165. 2. Gomes AS, Baker JD, Martin-Paredero V, et al. Acute renal dysfunction after major arteriography. *AJR.* 1985; 145:1249-1253.

*Omnipaque® (iohexol) — Winthrop Pharmaceuticals
†Isovue® (iopamidol) — E.R. Squibb & Sons, Inc.

Please see the following page for a brief summary of prescribing information.

Nonionic
OPTIRAY®
(ioversol)

A safer way to great imaging

OPTIRAY® 160 240 320 350
(Ioversol Injection)

DESCRIPTION: Each milliliter of OPTIRAY 160 (ioversol injection 34%) provides 339 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 160 provides 16% (160 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 240 (ioversol injection 51%) provides 509 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 240 provides 24% (240 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 320 (ioversol injection 68%) provides 673 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 320 provides 32% (320 mg/mL) organically bound iodine.

Each milliliter of OPTIRAY 350 (ioversol injection 74%) provides 741 mg of ioversol with 3.6 mg of tromethamine as a buffer and 0.2 mg of edetate calcium disodium as a stabilizer. OPTIRAY 350 provides 35% (350 mg/mL) organically bound iodine.

CONTRAINDICATIONS: None.

WARNINGS: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state and concomitant medications may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

Serious or fatal reactions have been associated with the administration of iodine-containing radiopaque media. It is of utmost importance to be completely prepared to treat any contrast medium reaction.

As with any contrast medium, serious neurologic sequelae, including permanent paralysis, can occur following cerebral arteriography, selective spinal arteriography and arteriography of vessels supplying the spinal cord. A cause-effect relationship to the contrast medium has not been established since the patients' pre-existing condition and procedural technique are causative factors in themselves. The arterial injection of a contrast medium should never be made following the administration of vasopressors since they strongly potentiate neurologic effects.

Caution must be exercised in patients with severely impaired renal function, combined renal and hepatic disease, severe thyrotoxicosis, myelomatosis, or anuria, particularly when large doses are administered.

Intravascularly administered iodine-containing radiopaque media are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Myeloma occurs most commonly in persons over age 40. Although neither the contrast agent nor dehydration has been proved separately to be the cause of anuria in myelomatous patients, it has been speculated that the combination of both may be causative. The risk in myelomatous patients is not a contraindication to the procedure; however, special precautions, including maintenance of normal hydration and close monitoring, are required. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The blood pressure should be assessed throughout the procedure, and measures for treatment of a hypertensive crisis should be available.

Contrast media may promote sickling in individuals who are homozygous for sickle cell disease when administered intravascularly.

Reports of thyroid storm following the intravascular use of iodinated radiopaque agents in patients with hyperthyroidism or with an autonomously functioning thyroid nodule, suggest that this additional risk be evaluated in such patients before use of any contrast medium.

PRECAUTIONS: *General:* Diagnostic procedures which involve the use of iodinated intravascular contrast agents should be carried out under the direction of personnel skilled and experienced in the particular procedure to be performed. A fully equipped emergency cart, or equivalent supplies and equipment, and personnel competent in recognizing and treating adverse reactions of all types should always be available. Since severe delayed reactions have been known to occur, emergency facilities and competent personnel should be available for at least 30 to 60 minutes after administration.

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, diabetic patients, and in susceptible non-diabetic patients (often elderly with pre-existing renal disease). *Patients should be well hydrated prior to and following the administration of OPTIRAY.*

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions, should always be considered (See ADVERSE REACTIONS). Increased risk is associated with a history of previous reaction to a contrast medium, a known sensitivity to iodine and known allergies (i.e., bronchial asthma, hay fever and food allergies) or hypersensitivities.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous to the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast medium, may be more accurate than pretesting in predicting potential adverse reactions. A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent when a diagnostic procedure is thought essential, but caution should be exercised. Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered. Reports indicate that such pretreatment does not prevent serious life-threatening reactions, but may reduce both their incidence and severity.

General anesthesia may be indicated in the performance of some procedures in selected patients; however, a higher incidence of adverse reactions has been reported in these patients, and may be attributable to the inability of the patient to identify untoward symptoms or to the hypotensive effect of anesthesia which can prolong the circulation time and increase the duration of exposure to the contrast agent.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be considered during catheter manipulations and contrast medium injection. Test injections to insure proper catheter placement are suggested.

Angiography should be avoided whenever possible in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

Patients with congestive heart failure should be observed for several hours following the procedure to detect delayed hemodynamic disturbances which may be associated with a transitory increase in the circulating osmotic load.

Selective coronary arteriography should be performed only in selected patients and those in whom the expected benefits outweigh the procedural risks.

Pulmonary angiography should be performed with caution in patients with severe pulmonary emphysema since the necessity for performing this procedure may be questionable.

Extreme caution during injection of a contrast medium is necessary to avoid extravasation. This is especially important in patients with severe arterial or venous disease.

Drug Interactions: Renal toxicity has been reported in a few patients with liver dysfunction who were given oral cholecystographic agents followed by intravascular contrast agents. Administration of any intravascular contrast agent should therefore be postponed in patients who have recently received a cholecystographic contrast agent.

Other drugs should not be mixed with ioversol injection.

Drug Laboratory Test Interactions: The results of PBI and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for up to 16 days following administration of iodinated contrast media. However, thyroid function tests not depending on iodine estimations, e.g., T3 resin uptake and total or free thyroxine (T4) assays are not affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long term animal studies have been performed to evaluate carcinogenic potential. However, animal studies suggest that this drug is not mutagenic and does not affect fertility.

Pregnancy Category B. No teratogenic effects attributable to ioversol have been observed in teratology studies performed in animals. There are, however, no adequate and well controlled studies in pregnant women. It is not known whether ioversol crosses the placental barrier or reaches fetal tissues. However, many injectable contrast agents cross the placental barrier in humans and appear to enter fetal tissue passively. Because animal teratology studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. X-ray procedures involve a certain risk related to the exposure of the fetus.

Nursing Mothers: It is not known whether ioversol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women because of potential adverse reactions, and consideration should be given to temporarily discontinuing nursing.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Adverse reactions following the use of OPTIRAY formulations are usually mild to moderate, of short duration and resolve spontaneously (without treatment). However, serious, life-threatening and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media.

Injections of contrast media are often associated with sensations of warmth and pain. In controlled double-blind clinical studies, significantly less warmth and pain were associated with the injection of OPTIRAY than with iothalamate meglumine, diatrizoate meglumine, and diatrizoate meglumine and diatrizoate sodium.

When OPTIRAY was used for coronary arteriography and ventriculography in double-blind clinical trials, electrocardiographic and hemodynamic changes occurred with less frequency and severity with ioversol injection than with diatrizoate meglumine and diatrizoate sodium.

Following coronary artery and left ventricular injection, electrocardiographic parameters were affected less with OPTIRAY (ioversol injection) than with diatrizoate meglumine and diatrizoate sodium injection. These parameters included the following: bradycardia, tachycardia, T-wave amplitude, ST depression and ST elevation.

OPTIRAY has also been shown to cause fewer changes in cardiac function and systemic blood pressure than conventional ionic media. These include cardiac output, left ventricular systolic and end-diastolic pressure, right ventricular systolic and pulmonary artery systolic pressures and decreases in systolic and diastolic blood pressures.

The following table of incidence of reactions is based upon clinical trials with OPTIRAY formulations in over 1466 patients. This listing includes all adverse reactions which were coincidental to the administration of ioversol regardless of their direct attributability to the drug or the procedure. Adverse reactions are listed by organ system and in decreasing order of occurrence. Significantly more severe reactions are listed before others in a system regardless of frequency.

Adverse Reactions

System	> 1%	≤ 1%
Cardiovascular	none	angina pectoris hypotension blood pressure fluctuation arterial spasm bradycardia conduction defect false aneurysm hypertension transient arrhythmia vascular trauma
Digestive	none	nausea vomiting
Nervous	none	cerebral infarct headache blurred vision vertigo lightheadedness vasovagal reaction disorientation paresthesia dysphasia muscle spasm syncope visual hallucination
Respiratory	none	laryngeal edema pulmonary edema sneezing nasal congestion coughing shortness of breath hypoxia
Skin	none	periorbital edema urticaria facial edema flush pruritus
Miscellaneous	none	extravasation hematoma shaking chills bad taste general pain

Regardless of the contrast medium employed, the overall incidence of serious adverse reaction is higher with coronary arteriography than with other procedures. Cardiac decompensation, serious arrhythmias, myocardial ischemia or myocardial infarction may occur during coronary arteriography and left ventriculography.

General Adverse Reactions to Contrast Media

The following adverse reactions are possible with any parenterally administered iodinated contrast medium. Severe life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. Most deaths occur during injection or 5 to 10 minutes later; the main feature being cardiac arrest with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The reported incidence of adverse reactions to contrast media in patients with conventional iodinated contrast agents range from 6.6 per 1 million (0.00066 percent) to 1 in 10,000 patients (0.01 percent).

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that of the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast medium, the dose and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the dose injected, the speed of injection, the mode of injection and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

In addition to the adverse reactions reported for ioversol, the following additional adverse reactions have been reported with the use of other contrast agents and are possible with any water soluble, iodinated contrast agent:

Nervous: convulsions, aphasia, paralysis, visual field losses which are usually transient but may be permanent, coma and death.

Cardiovascular: angioneurotic edema, peripheral edema, vasodilation, thrombosis and rarely thrombophlebitis, disseminated intravascular coagulation and shock.

Skin: maculopapular rash, erythema, conjunctival symptoms, ecchymosis and tissue necrosis.

Respiratory: choking, dyspnea, wheezing which may be an initial manifestation of more severe and infrequent reactions including asthmatic attack, laryngospasm and bronchospasm, apnea and cyanosis. Rarely these allergic-type reactions can progress into anaphylaxis with loss of consciousness, coma, severe cardiovascular disturbances and death.

Miscellaneous: hyperthermia, temporary anuria or other nephropathy.

Other reactions may also occur with the use of any contrast agent as a consequence of the procedural hazard; these include hemorrhage or pseudoaneurysms at the puncture site, brachial plexus palsy following axillary artery injections, chest pain, myocardial infarction, and transient changes in hepatorenal chemistry tests. Arterial thrombosis, displacement of arterial plaques, venous thrombosis, dissection of the coronary vessels and transient sinus arrest are rare complications.

In cerebral arteriography, cardiovascular reactions that may occur with some frecuency are bradycardia and either an increase or decrease in systemic blood pressure. Neurological reactions that may occur are: seizures, drowsiness, transient paresis, and mild disturbances in vision.

Central nervous system reactions with OPTIRAY in controlled clinical studies in cerebral arteriography that were considered drug-related and occurred with frequencies greater than 1% were: headache, bradycardia, blood pressure fluctuation, disorientation, nausea and vertigo.

In aortography, depending on the technique employed, the risks of this procedure also include the following: injury to the aorta and neighboring organs, pleural puncture, renal damage including infarction and acute tubular necrosis with oliguria and anuria, retroperitoneal hemorrhage from the translumbar approach and spinal cord injury and pathology associated with the syndrome of transverse myelitis. Under conditions of slowed aortic circulation there is an increased likelihood for aortography to cause muscle spasm. Occasional serious neurologic complications, including paraplegia, have also been reported in patients with aortoiliac obstruction, femoral artery obstruction, abdominal compression, hypotension, hypertension, spinal anesthesia, and injection of vasopressors to increase contrast. In these patients the concentration, volume, and number of repeat injections of the medium should be maintained at a minimum with appropriate intervals between injections. The position of the patient and catheter tip should be carefully monitored.

Entry of a large aortic dose into the renal artery may cause, even in the absence of symptoms, albuminuria, hematuria, and an elevated creatinine and urea nitrogen. Rapid and complete return of function usually follows.

There were no cardiovascular system reactions with OPTIRAY in controlled clinical studies in coronary arteriography with left ventriculography that were considered drug-related and occurred with a frequency greater than 1%.

PRECAUTIONS FOR SPECIFIC PROCEDURES:

Cerebral Arteriography

Extreme caution is advised in patients with advanced arteriosclerosis, severe hypertension, cardiac decompensation, senility, recent cerebral thrombosis or embolism, and migraine.

Peripheral Arteriography

Pulsation should be present in the artery to be injected. In thromboangiitis obliterans, or ascending infection associated with severe ischemia, angiography should be performed with extreme caution, if at all.

Coronary Arteriography and Left Ventriculography

Mandatory prerequisites to the procedure are specialized personnel, ECG monitoring apparatus and adequate facilities for immediate resuscitation and cardioversion. Electrocardiograms and vital signs should be routinely monitored throughout the procedure.

Venography

Special care is required when venography is performed in patients with suspected thrombosis, phlebitis, severe ischemic disease, local infection or a totally obstructed venous system. In order to minimize extravasation during injection, fluoroscopy is recommended.

Intravenous Digital Subtraction Angiography

In addition to the general precautions previously described, the risks associated with IV DSA include those usually attendant with catheter procedures and include intramural injections, vessel dissection and tissue extravasation. The potential risk is reduced when small test injections of contrast medium are made under fluoroscopic observation to insure that the catheter tip is properly positioned and, in the case of peripheral placement, that the vein is of adequate size.

Patient motion, including respiration and swallowing, can result in misregistration leading to image degradation and non-diagnostic studies.

OVERDOSAGE: The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular system. Treatment of an overdosage is directed toward the support of all vital functions, and prompt institution of symptomatic therapy.

Ioversol does not bind to plasma or serum protein and is therefore, dialyzable.

The intravenous LD_{50} values (gI/kg) for ioversol in animals were: 17 (mice), and 15 (rats).

DOSAGE AND ADMINISTRATION: Details on dosage are provided in the package insert. CONSULT FULL PACKAGE INSERT BEFORE USE.

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Comparative Clinical Consequences of Aggressive Lipid Management, Coronary Angioplasty and Bypass Surgery in Coronary Artery Disease

Robert A. Vogel, MD

Current management of coronary artery disease consists almost exclusively of medical therapy designed to reduce myocardial oxygen consumption, and angioplasty and bypass surgery designed to increase myocardial oxygen delivery. The minority of coronary disease patients receives therapy to change the atherosclerotic process,[1] although antiplatelet therapy (demonstrated to reduce thrombotic vessel occlusion) is often prescribed after angioplasty, bypass surgery and acute myocardial infarction.[2] Several recent studies demonstrated that aggressive lipid management can accomplish the same treatment goals as traditional antianginal and interventional therapy (i.e., reduction in arteriographic stenosis, disease progression, anginal frequency, exercise intolerance, cardiovascular events and mortality).[3-15] This review compares the clinical consequences of aggressive lipid management (30% cholesterol reduction) with those achieved by coronary angioplasty and bypass surgery on these important parameters. Although no direct comparisons have been reported, data presented are the consensus of multiple controlled studies.

Coronary stenosis: Several forms of evidence suggest that lipid abnormalities have pivotal roles in the development of atherosclerosis and that favorable consequences result from lipid modification. These are summarized in Table I, and in previous editorials and reviews.[16-18] Important observations are that atherosclerosis is experimentally inducible in certain species, and clinically correlated with high fat and cholesterol content diets. Regression of experimental and clinical atherosclerosis, and reduced disease progression follow dietary changes.[19-26] Five recently published clinical studies using different aggressive means for altering serum lipids also demonstrated both coronary disease regression and reduction in disease progression.[7-12] In 1987, Blankenhorn et al[7] reported the results of a randomized angiographic trial in 162 nonsmoking middle-aged men with previous coronary bypass surgery (Cholesterol Lowering Atherosclerosis Study [CLAS]).[8] Patients receiving colestipol and nicotinic acid were found to have an 18% incidence of improved coronary disease score by visually interpreted arteriography versus 2% in control patients. Progression of disease was also significantly lessened (61 vs 39%). Importantly, retrospective analysis demonstrated equal benefit for patients with high and normal total and low-density lipoprotein cholesterols at baseline.[27]

The effects of an aggressive lifestyle modification program (consisting of a strict vegetarian diet, smoking cessation, stress management and moderate exercise) on the natural history of coronary artery disease was reported by Ornish et al[11] in a 48-patient, randomized trial (Lifestyle Heart Trial). Mean percent diameter stenosis (measured by quantitative arteriography) improved from 40 to 38% in the treatment group, but progressed from 43 to 46% in the control group. Lesions >50% underwent a greater degree of regression (61 to 56%). In all, 82% of the treated patients had less coronary disease at the end of the 1-year trial. Coronary flow reserve (measured by positron emission tomography) improved 6% in the treated patients.[6]

Buchwald et al[9] reported a long-term randomized trial that tested whether cholesterol-lowering induced by partial ileal bypass surgery would favorably affect postmyocardial infarction patients (Program on the Surgical Control of the Hyperlipidemias [POSCH]). The 838 patients were followed for a mean period of 9.7 years. Significantly fewer ileal-bypassed patients experienced myocardial infarction or cardiac death.

Brown et al[10] reported the results of aggressive pharmacologic lipid intervention in 146 men with family histories of vascular disease and apolipoprotein B levels >125 mg/dl (Familial Atherosclerosis Treatment Study [FATS]). Patients were randomized to placebo (or colestipol if the low-density lipoprotein cholesterol level was increased), lovastatin and colestipol, or niacin and colestipol treatment groups. Quantitatively measured mean percent diameter narrowing progressed 2% during 2.5 years in the dietary-managed patients compared with a mean regression of 0.3 and 1.1% in the lovastatin plus colestipol and nicotinic acid plus colestipol treatment groups, respectively. A greater extent of regression was observed in lesions with >50% diameter narrowing (2.6, 6.4% for the 2 drug treatment groups). Multivariant analysis demonstrated that a reduction in the level of apolipoprotein B, low-density lipoprotein cholesterol and systolic blood pressure, and an increase in high-density lipoprotein cholesterol correlated independently with regression of coronary lesions. The 2 aggressive management groups had 75% fewer cardiovascular events (mostly unstable angina) than did the diet-treated group.

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TABLE I Evidence Linking Cholesterol to Coronary Atherosclerosis

Nature of Evidence
Experimental
Cholesterol present in atheromas[19]
High dietary cholesterol/lipid levels induces atherosclerosis[19–21]
Reduction in dietary lipid regresses atherosclerosis[20,21]
Epidemiologic
CAD prevalence correlates with serum/dietary cholesterol levels[22,23]
Low incidence of CAD in people subjected to dietary deprivation or wasting illnesses[24,25]
Clinical trials
Reduction in dietary cholesterol/lipid regresses atherosclerosis and slows disease progression[11,26]
Surgical cholesterol lowering regresses atherosclerosis and slows disease progression[9]
Pharmacologic lipoprotein modification regresses atherosclerosis and reduces CV events[3,5,10,12]
Pharmacologic lipoprotein modification (sufficient magnitude) decreases mortality[13,14]

CAD = coronary artery disease; CV = cardiovascular.

Disease regression (2% mean lesion stenosis) was also found by Kane et al[12] in a 72-patient multiple-drug quantitative arteriographic study. The overall group with established disease was shown to benefit. Taken as a group, these 5 major studies suggest that coronary atherosclerosis is at least partly reversible and that progression of disease lessened with aggressive lipid management, independent of the means by which it was achieved (Table II). Strict dietary therapy appears to be at least as effective as drug therapy, and can be provided at a lower cost and potential risk. With 2 years of diet or drug therapy, or both, hemodynamically significant lesions (>50% stenosis) regress approximately 5% (mean of Lifestyle Heart and FATS data).

Coronary angioplasty appears to provide a greater magnitude of stenosis reduction than does lipid modification, although this is limited to the target vessels. Approximately 90% of attempted dilatations are currently successful, with visually estimated percent diameter stenosis decreasing from approximately 80 to 20%.[28–30] However, postangioplasty assessment is often complicated by the presence of dissection or intraluminal thrombus, or both.[31] Quantitative coronary arteriographic improvement in coronary anatomy is less dramatic (approximately 65 to 30%).[29,31] Moreover, 3 to 5% of stenoses occlude in the postinterventional period, and 30 to 50% undergo restenosis.[28,32,33] Additionally, narrowing is induced in the dilated "normal" segment adjacent to the lesion, leading to an underappreciation of the true degree of restenosis using percent diameter assessment.[34] At 6 to 12 months after angioplasty, lesion percent diameter stenosis remains improved only approximately 25% if successful and unsuccessful dilatations, occluded vessels and restenosed lesions are considered.[33,35] Lesions not dilated will progress at approximately 1%/year without other therapy.[10]

Coronary bypass surgery affects native coronary arteries through the occurrence of anastomotic narrowings, and progression of disease in the arteries proximal to graft insertion.[36,37] Myocardial infarction often accompanies parent artery occlusion.[38] These adverse consequences are balanced by the provision of collateral flow distal to the anastomosis as long as grafts remain patent. Comparative changes provided by aggressive lipid management, angioplasty and bypass surgery on coronary stenosis of lesions >50%, blood flow, exercise capacity, cardiovascular event rate and mortality are summarized in Table III and further discussed later.

Coronary blood flow: Using an animal model, Armstrong et al[39] demonstrated regional variability in minimum vascular resistance changes associated with atherosclerosis regression. Minimal coronary resistance improved 20% over 18 months. A 6% coronary flow reserve improvement was found using positron emission tomography in the Lifestyle Heart Trial over 1 year, together with a 91% reduction in anginal frequency.[6] Improvement in coronary flow reserve with aggressive lipid management is further supported by the preliminary findings of Zhukova et al[4] who demonstrated a 50% decrease in angina after 2 years of lovastatin therapy, associated with a 9% increase in treadmill exercise tolerance. Functional improvement was also observed in the Lipid Research Clinics Coronary Primary Prevention Trial,[3] in which cholestyramine was found to decrease angina by 20%, and abnormal stress electrocardiography by 25%.

Angioplasty improves flow physiology more than does lipid management, although its effects are limited

TABLE II Results of Recent Randomized Controlled Coronary Artery Disease Regression Trials

Study	Patients	Intervention	Regression Findings
CLAS[7,8,27]	162	Colestipol + niacin	18% of pts. had improved CAD score at 4 years
Lifestyle Heart Trial[6,11]	48	Strict diet, stop smoking, stress mgmt., exercise	2% mean lesion regression (5% regression in lesions >50%)
POSCH[9]	838	Partial ileal bypass	14% of pts. had improved CAD score at 7 years
FATS[10]	146	Colestipol + lovastatin or niacin	1% mean lesion regression (3 to 6% regression in lesions >50%)
Combined Drug Regimen Trial[12]	72	Colestipol ± niacin ± lovastatin	2% mean lesion regression

CAD = coronary artery disease; CLAS = Cholesterol Lowering Atherosclerosis Study; FATS = Familial Atherosclerosis Treatment Study; mgmt. = management; POSCH = Program on the Surgical Control of the Hyperlipidemias.

to the target vessel.[30,40–43] Coronary flow reserve improves from approximately 1.5 to 2.5 immediately after successful dilatation. Individual patient improvement does not appear to predict long-term clinical efficacy, probably owing to a combination of an initial, transient increase in resting blood flow and eventful restenosis.[42,44,45] Six months after angioplasty, coronary flow reserve in nonrestenosed distributions increases further to approximately 3, but remains below normal (>3.5). Work capacity on exercise testing improves substantially after angioplasty (25 to 60%), which was found to be superior to antianginal medical therapy in the first reported randomized angioplasty trial.[46,47] Including adverse outcomes, angioplasty improves flow reserve and exercise tolerance approximately 60 and 40%, respectively.

As with angioplasty, coronary bypass surgery significantly improves flow reserve, although complete normalization even with widely patent grafts has been variably demonstrated.[40,48] This finding appears to be owing to vasoregulatory and regional ventricular dysfunctions.[48] Coronary flow reserve late after bypass surgery is approximately 3 in the 90% of grafts that remain patent at 1 year. Exercise capacity increases approximately 50% (40 to 80%) after bypass surgery, which has been shown to significantly reduce anginal frequency as compared with antianginal management.[46,49] However, lipid treatment, which also reduces anginal frequency significantly (50 to 91%, see aforementioned), has generally not been used in the surgery versus medical therapy trials. Including adverse outcomes, bypass surgery improves flow reserve and exercise tolerance approximately 90 and 40%, respectively.

Nonfatal cardiovascular events: Large prospective, randomized trials demonstrated that nonfatal cardiovascular events, such as acute myocardial infarction and need for bypass surgery, are reduced proportional to lipid modification.[3,5] In general, a 2% decrease in cardiovascular events results from each 1% reduction in low-density lipoprotein cholesterol, or increase in high-density lipoprotein cholesterol. Much of these data were obtained in primary prevention trials studying middle-aged men with increased cholesterol levels. Considerably less is known about primary prevention in women, younger and older subjects, and those with lesser cholesterol increases. In general, more data are available supporting low- than high-density cholesterol modification, because the latter is difficult to achieve alone. Secondary prevention trials of lipid modification demonstrated reductions in cardiovascular events at least as great as those of primary prevention trials.[50,51] A 45% reduction in suspected or proven nonfatal myocardial infarction was found in the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial.[9] In the FATS Trial, a 75% reduction in cardiovascular events was found.[10] However, this was a small trial (146 men), and most of the adverse episodes were unstable angina. Overall, aggressive lipid modification (30% cholesterol reduction) appears to reduce cardiovascular event rate frequency approximately 50% over 5 years.

It is much more difficult to determine the change in subsequent events in patients undergoing coronary angioplasty. Data from the small Veterans Administration Angioplasty Compared with Medical Therapy trial[47] on this variable are not yet available, and most other randomized trials of angioplasty were comparisons with bypass surgery. However, uncontrolled clinical experience suggests that long-term outcome is generally good.[28,52]

TABLE III Comparative Clinical Consequences of Treatment

	Aggressive Lipid Management*	Coronary Angioplasty	Bypass Surgery
Coronary artery stenosis (lesions > 50%, 2 years)	−5%	−25%	†
Coronary flow reserve (1 year)	6%	60%	90%
Exercise capacity (2 years)	10%	40%	50%
Nonfatal cardiovascular events (5 years)	−50%	Unknown	16%
Survival (10 years)	10%	Unknown	8%‡

*Approximate 30% cholesterol reduction.
†Accelerates proximal vessel stenosis, but provides collateral revascularization.
‡Depending on presence of high-risk features.

Coronary bypass surgery has been found to increase subsequent myocardial infarction frequency by 16%, but survival is improved despite this complication, probably owing to the provision of collateral flow.[53] The increase in infarction rate is mostly due to perioperative, and late proximal vessel and graft closures.[36,37]

Mortality: It has been difficult to demonstrate a change in overall mortality in primary prevention trials using lipid modification, but total mortality appears to decrease in patients with established disease if substantial lipid modification is achieved.[13,14,50,51] In a recently published review of primary and secondary trials, Holme[14] demonstrated a relation between decreasing serum cholesterol and total mortality, which suggests benefit with aggressive treatment. The niacin treatment group in the Coronary Drug Project[13] had an 11% reduction in overall mortality compared with that of the control group after 15 years, although the former had received drug treatment only during the study's first 5 years. Although not statistically significant, the POSCH trial reported a 21% reduction in overall mortality with ileal bypass.[9] These data conservatively suggest an approximate 10% increase in survival with aggressive lipid management over approximately 10 years.

An estimate of the effect of angioplasty on mortality in the near future is unlikely, because no current trial has sufficient size, and only the ACME trial has a medical management control group.

Overall mortality was not affected by early experience bypass surgery compared with medical management, although specific factors such as left main stenosis, extensive multivessel disease, left ventricular dysfunction and positive stress tests predict surgical benefit.[49,54–56] More recent surgery appears to provide greater survival benefit, estimated at 8% over 10 years.[56]

Antianginal therapy: Antianginal medical therapy appears to have little effect on atherosclerosis, although

cardiovascular events and mortality may be reduced. One exception is the decrease in the appearance of new lesions with nifedipine therapy.[57] A decrease in mortality after non-Q-wave infarction in patients without heart failure treated with diltiazem has been reported,[58] and a decrease in mortality in those with Q-wave infarction treated with β-adrenergic blocker therapy is well established.[59] Despite pharmacologic and interventional advances, most of the reduction in coronary disease mortality over the past few decades appears due to reductions in smoking, hypertension and hyperlipidemia.[60]

Comparative consequences: The clinical consequences of aggressive lipid management, angioplasty and bypass surgery are compared in Table III. Coronary stenosis, flow reserve and exercise tolerance are generally managed more effectively by angioplasty and bypass surgery. In contrast, reductions in nonfatal cardiovascular events and survival appear to be better achieved with lipid management, although subgroups do well with bypass surgery. This result is likely due to "stabilization" of lesions with lipid modification and to provision of collaterals with bypass surgery, rather than to reduction in coronary stenosis. Unfortunately, aggressive lipid management is not provided to many patients with established disease[1] or to those undergoing coronary artery interventions. Preliminary data suggest some value for cholesterol reduction on postangioplasty restenosis, although larger studies are needed to confirm this finding.[61] Lipid abnormalities clearly affect bypass graft disease progression and patency.[62] Some established graft disease appears to be reversible with lipid management.[7,8] Taken together, these data suggest that most patients with coronary disease would benefit from aggressive lipid management associated with judicious use of interventional therapy. More data are needed to establish the benefit of lipid modification in patients with "desirable" (<200 mg/dl) cholesterol levels and to define the optimal magnitude of modification. In the absence of a direct comparison of these therapies, available data support a broader use of lipid modification to achieve the traditional goals of coronary artery disease management.

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Potential Limitations of Percutaneous Transluminal Coronary Angioplasty in Heart Transplant Recipients

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The number of patients undergoing transplantation for terminal heart failure has increased dramatically over the last few years.[1] Occlusive coronary artery disease has emerged as a major cause of late graft loss.[2] The only viable alternative for heart transplant recipients with progressive coronary disease has been retransplantation.[3] The role of percutaneous transluminal coronary angioplasty (PTCA) in this patient population remains undefined. This study reviews our experience with PTCA in this patient population.

Between January 1980 and October 1989, 501 patients underwent orthotopic heart or heart/lung transplantation at our institution. The immunosuppressive regimen included cyclosporine in all these patients. Coronary angiography is routinely performed on an annual basis. The prevalence of any apparent occlusive coronary artery disease by angiography was 5% at 1, 17% at 2, 26% at 3, 40% at 4 and 52% at 5 years. Of patients with coronary disease, 8 (6 men and 2 women; 7 orthotopic heart and 1 heart/lung transplant) were considered suitable candidates for PTCA because of the presence of proximal and focal coronary disease. The rest did not have disease that would be considered technically suitable for PTCA, or if they did, it occurred in conjunction with severe and diffuse disease of the distal vessel. Mean age at transplantation of the 8 patients who underwent PTCA was 37 ± 10 years. The indication for transplantation was idiopathic cardiomyopathy in 4, ischemic cardiomyopathy in 2, and irreversible congestive heart failure due to valvular disease in 1. One patient underwent heart/lung transplantation for primary pulmonary hypertension. The mean age of the donor hearts was 26 ± 9 years. The focal and proximal disease subjected to PTCA was not present on the first annual coronary angiograms after transplantation and was thus not present in the donor hearts before transplantation.

Initial PTCA was performed 43 ± 19 months (range 26 to 78) after transplantation. Indications for PTCA included (1) reversible exercise-induced thallium defects (4 procedures); (2) symptoms, particularly exercise-induced dyspnea, potentially attributable to coronary artery stenosis (4 procedures); (3) "silent" ST elevation during ambulatory electrocardiographic monitoring (1 procedure); or (4) restenosis of a prior PTCA site (1 procedure). An additional procedure was performed in an attempt to open a chronic total occlusion in an asymptomatic patient with progressive multivessel coronary artery disease. All procedures were performed with standard over-the-wire steerable dilatation systems using systemic anticoagulation with heparin.[4] Gradients before and after dilatation were measured for 8 lesions. To quantify the number of vessels involved in follow-up coronary angiograms, significant coronary artery disease was defined as a 50% reduction in luminal diameter of a large epicardial vessel, although admittedly, this can be a difficult determination to make in some heart transplant patients because of diffuse involvement of the affected vessels.

A total of 11 PTCA procedures were performed on 8 patients. Six underwent a single procedure, 1 underwent 2 procedures and 1 underwent 3 procedures. A total of 13 lesions were attempted. The distribution of the lesions was 8 (62%) in the left anterior descending/diagonal

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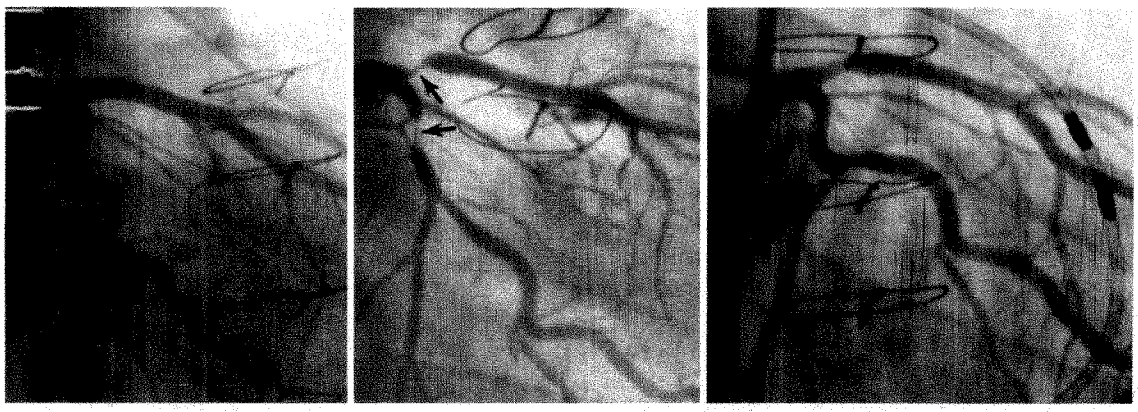


FIGURE 1. Left coronary angiograms in right anterior oblique projection. *Left,* no discernible disease 11 months after transplantation. *Middle,* performed 60 months after transplantation demonstrates focal high-grade lesions *(arrows)* in the proximal left anterior descending and circumflex arteries. *Right,* successful immediate outcome of percutaneous transluminal coronary angioplasty. A stress thallium was negative for ischemia 5 months later. The patient died suddenly 10 months after angioplasty.

coronary arteries, 2 (15%) in the circumflex coronary artery and 3 (23%) in the right coronary artery. Two of the attempted lesions were total occlusions. Twelve of the 13 lesions were primary lesions. One was considered to be a restenosis being diagnosed 5 months after initial PTCA.

Initial angiographic success was achieved in 11 of the 13 attempted lesions. Both unsuccessful attempts occurred due to the inability to cross total occlusions with a guidewire. For successfully dilated lesions, mean stenosis was reduced from 85 ± 6 to 30 ± 8% ($p < 0.001$). The mean pressure gradient across the lesion decreased from 54 ± 15 to 18 ± 10 mm Hg ($p < 0.001$). Figures 1, 2 and 3 illustrate the immediate result of angioplasty in 3 patients. One patient developed ventricular fibrillation during PTCA due to diffuse spasm of the dilated artery that was treated with electrical cardioversion and intracoronary nitroglycerin. There were no other acute complications.

Of 10 successfully dilated primary lesions, 6 were restudied 4 or more months after PTCA. One was considered to have restenosed, repeat PTCA was successful-

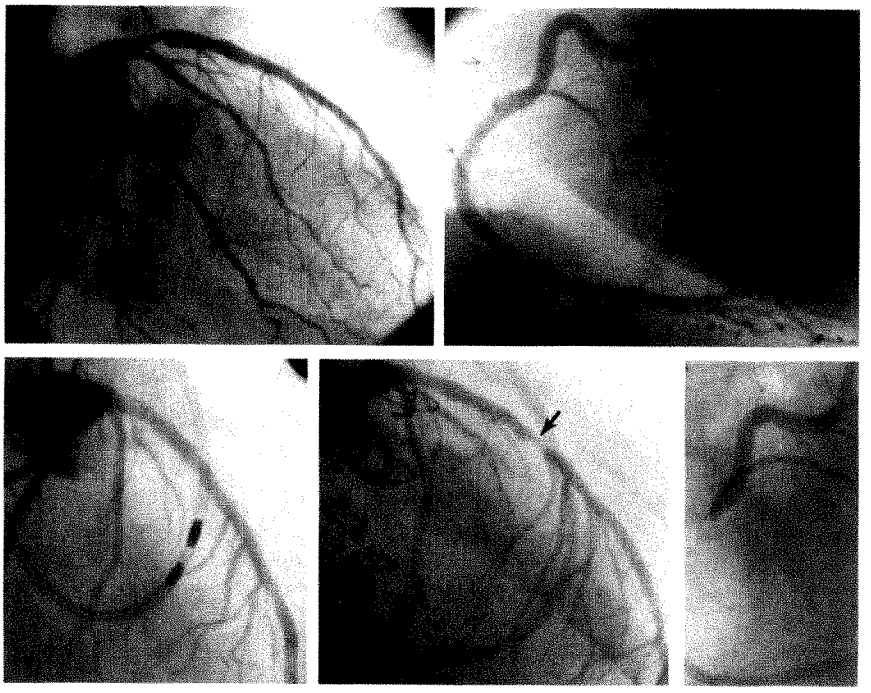


FIGURE 2. ***Top left,*** **left coronary angiogram in right anterior oblique projection;** ***top right,*** **right coronary angiogram in left anterior oblique projection in a patient 35 months after transplantation. There is a high-grade lesion** ***(arrow)*** **in the proximal left anterior descending artery.** ***Bottom left,*** **successful immediate outcome of percutaneous transluminal coronary angioplasty.** ***Bottom middle and right,*** **angiograms of the left and right coronary arteries, respectively, 32 months after percutaneous transluminal coronary angioplasty when congestive heart failure developed.** ***Bottom middle,*** **progression of disease** ***(arrow)*** **in the mid left anterior descending artery;** ***bottom right,*** **total occlusion of the right coronary artery. The patient died suddenly 4 months later.**

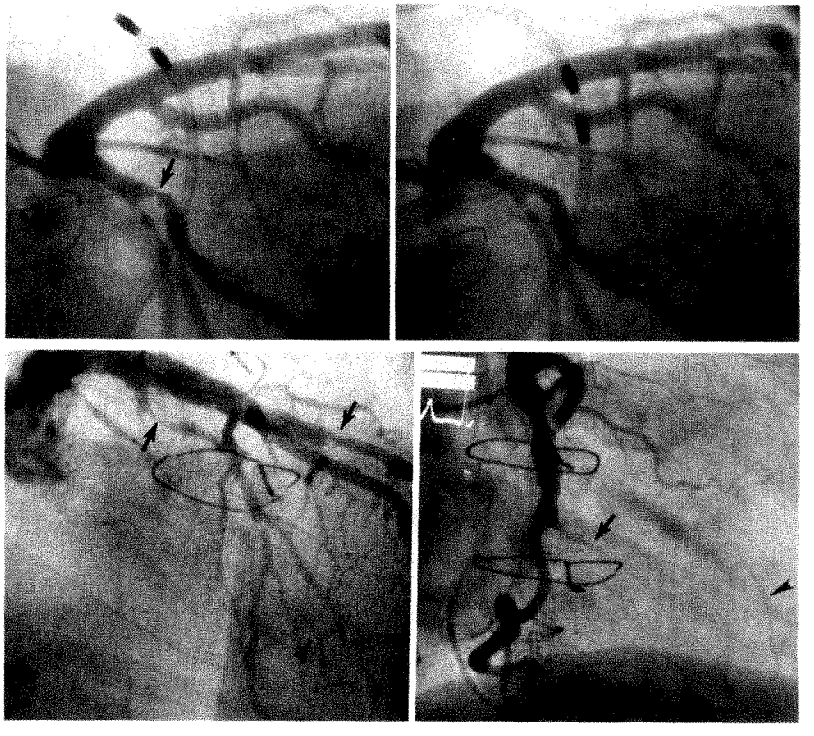


FIGURE 3. ***Top left,*** **left coronary angiogram in right anterior oblique projection of a patient 36 months after transplantation. A high-grade focal lesion** ***(arrow)*** **is present in an obtuse marginal branch.** ***Top right,*** **successful immediate outcome of percutaneous transluminal coronary angioplasty.** ***Bottom left and right,*** **angiograms of the left and right coronary arteries, respectively, both in right anterior oblique projection, 40 months after percutaneous transluminal coronary angioplasty when the patient was asymptomatic.** ***Bottom left,*** **the circumflex artery is occluded proximally, and there is progression of disease in the left anterior descending/diagonal system** ***(arrows);*** **in addition there is collateral flow to an acute marginal branch of the right coronary artery** ***(arrowhead).*** ***Bottom right,*** **diffuse disease of the right coronary artery with occlusion of a large acute marginal branch** ***(arrow);*** **in addition there is collateral flow to the occluded circumflex system** ***(arrowheads).*** **The ventriculogram obtained concurrently with** ***bottom left and right*** **revealed new akinesia of the inferior wall.**

TABLE I Long-Term Outcome of Heart Transplant Recipients Undergoing Percutaneous Transluminal Coronary Angioplasty

Pt.	Sex	Age at Transplant (yr)	Time of Initial PTCA (mo)	Post-PTCA Follow-Up (mo)	Status	Comment
1	Male	54	31	3	Dead	Death from progressive CHF
2	Male	28	52	4	Dead	Sudden death; site of PTCA widely patent 16 days before death
3	Male	38	60	10	Dead	Sudden death
4	Female	28	26	12	Alive	No cardiac symptoms; progressive CAD by angiography
5	Male	41	26	15	Alive	MI with CHF 9 months after PTCA; resuscitated from sudden death at 15 months; NYHA class III
6	Male	37	78	35	Alive	No cardiac symptoms; progressive CAD by angiography
7	Female	23	35	36	Dead	MI with CHF at 32 months after PTCA; sudden death
8	Male	43	39	40	Alive	No cardiac symptoms; new inferior akinesia and progressive CAD by angiography at 40 months after PTCA

CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; NYHA = New York Heart Association classification; PTCA = percutaneous transluminal coronary angioplasty.

ly performed and at restudy no restenosis had occurred. An additional lesion could not be evaluated for restenosis because of occlusion of the proximal portion of the coronary artery. The other 4 PTCA sites remained widely patent at repeat coronary angiography.

In long-term clinical follow-up, 4 patients have died (Table I). Three died suddenly 4, 10 and 36 months after initial PTCA. Another died of progressive congestive heart failure 3 months after PTCA. Autopsy examination in 2 patients (Figure 4) revealed diffuse and extensive intimal fibromuscular hyperplasia of coronary arteries with no discernible histologic difference at PTCA sites. A fifth patient is alive 15 months after PTCA but requires aggressive treatment for congestive heart failure. This patient sustained a myocardial infarction 9 months after PTCA from disease distant to the PTCA site. He has been resuscitated from an episode of sudden death due to ventricular tachycardia.

Three patients remain free of symptoms 12, 35 and 40 months after initial PTCA. However, repeat angiography in all 3 has demonstrated progressive diffuse coronary disease. One of these 3 is the only patient in this series with well-established collateral channels and this may account for his asymptomatic state (Figure 3). All 3 of these patients had significant 1-vessel disease at the time of initial PTCA, but at follow-up 2 have developed significant 2-vessel disease and 1 has developed significant 3-vessel disease.

Whereas most heart transplant recipients with occlusive coronary artery disease have diffuse disease involving the distal smaller epicardial arteries visualized at angiography,[5] patients with proximal, focal and severe occlusive lesions may also be identified in individual cases. Data on the use of PTCA in these patients is limited to either single case reports or short clinical follow-up.[6–9] The initial angiographic lesional success rate (85%) in our series

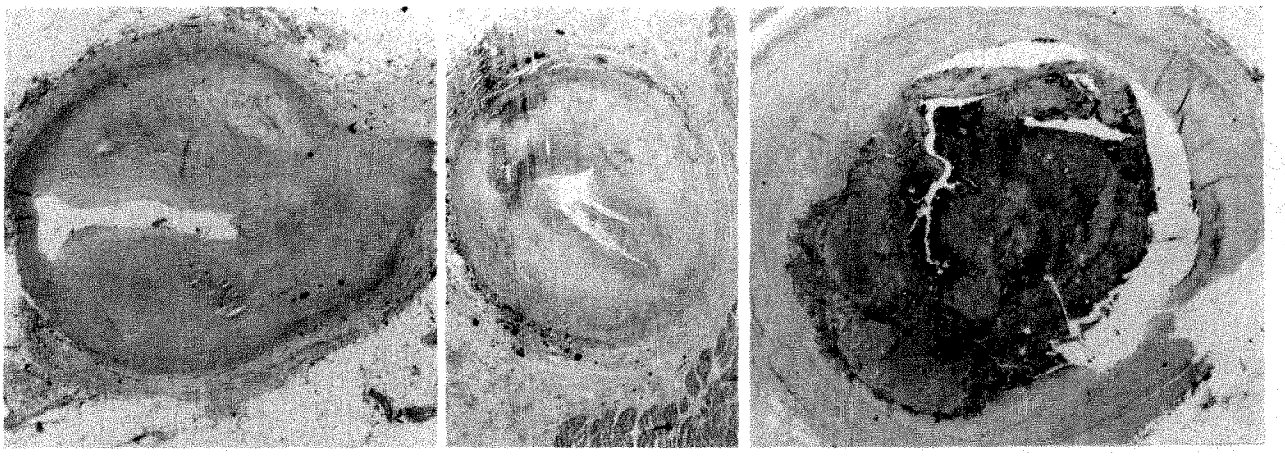


FIGURE 4. Photomicrographs (hematoxylin-eosin stain) of cross sections of midportions of coronary arteries of a patient who died in follow-up: *left*, left anterior descending artery; *middle*, circumflex artery; *right*, right coronary artery. All sections demonstrate advanced fibromuscular hyperplasia with focal atheromateus degeneration. *Right*, premortem thrombus completely occludes the lumen.

of 8 patients undergoing attempted PTCA of 13 lesions during 11 procedures is similar to the previously reported 7 patients. All subtotal stenoses were successfully dilated. Only the 2 total occlusions could not be dilated, which is in keeping with the relatively low success rate with total occlusions in patients who have not undergone transplantation.[4]

However, the long-term follow-up of these patients has yielded dismal clinical results. Four patients have died and 1 is symptomatic from congestive heart failure and has been resuscitated from sudden death. These data suggest that once angiographic high-grade proximal coronary artery disease is detected, the prognosis for long-term graft survival is guarded. Despite improvement in functional studies (exercise-induced thallium defects) in some patients in the short term, it is uncertain if PTCA prolongs graft survival. For lack of conclusive data at the present time, this center is continuing to perform PTCA in transplant patients with focal proximal disease in the presence of symptoms, exercise-induced thallium defects or ischemic electrocardiographic changes during ambulatory monitoring; this is followed by frequent angiographic and clinical evaluation. An aggressive strategy of retransplantation is recommended for suitable candidates, albeit the shortage of donor hearts and the less favorable outcome associated with retransplantation.[3]

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Immediate Procedural and Long-Term Clinical Results of Internal Mammary Artery Angioplasty

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Internal mammary artery angioplasty has been used as an alternative to repeat operation in patients with symptom recurrence after coronary bypass grafting. With use of standard balloon techniques, procedural success rates of 90 to 94% have been obtained,[1–4] but the limited number of patients with an unsuccessful angioplasty attempt has precluded analysis of factors affecting immediate procedural success and complication rates. Long-term follow-up of these patients has often been limited and difficult to interpret owing to infrequent repeat coronary arteriography and the presence of multivessel coronary artery disease.[1–6] To identify the factors affecting immediate procedural success and to characterize the long-term outcome of patients undergoing internal mammary angioplasty, we reviewed our experience with this procedure over an 18-month period.

From January 1, 1990, to June 30, 1991, coronary angioplasty was performed during 3,431 procedures at the Washington Hospital Center; 22 procedures (0.6%) in 20 patients involved 24 lesions within the right (n = 2) or left (n = 22) internal mammary artery. The clinical characteristics of these patients, including age, gender, the presence of diabetes and bypass graft age (in months), were recorded from hospital chart review. Angina before the procedure was classified as unstable if pain occurred at rest and was scored before and after the procedure according to New York Heart Association functional classification criteria. Recent myocardial infarction was defined as enzymatic or electrocardiographic evidence of myocardial necrosis within 6 weeks of the procedure.

Before coronary angioplasty, all patients were pretreated with aspirin and, in most cases, a calcium antagonist. All procedures were performed by way of the right or left femoral artery using a 7 to 8Fr internal mammary or Judkins Right-4 guiding catheter using standard balloon methods. Heparin, 10,000 to 15,000 U, was administered at the beginning of the procedure with further intravenous bolus doses administered as needed to maintain the activated clotting time of >300 seconds. In the absence of coronary dissection, intravenous heparin was discontinued at the end of the procedure. Cineangiograms were reviewed using standard morphologic criteria[5]; angiographic success was defined as final caliper-determined diameter stenosis ≤50% with no in-hospital ischemic complications. Clinical follow-up was obtained in 18 of 20 patients (90%) 12.2 ± 4.6 months after angioplasty.

Immediate angiographic success was obtained in 20 of 24 lesions (83%) (Table I). An unsuccessful attempt was due to inability to cross the lesion with the guidewire in 3 patients and lesion rigidity in 1. No patient had in-

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TABLE I Clinical Characteristics of Patients Undergoing Internal Mammary Angioplasty

Pt.	Age (yr) & Sex	Diabetes Mellitus	Unstable Angina	Recent MI	Months After Bypass	Lesion Location Within Internal Mammary-Vessel Grafted	Pre % Diameter Stenosis	Post % Diameter Stenosis
				Successful				
1	58F	+	–	–	48	D-LAD	80	5
2	59F	–	+	–	48	P, mid, D-LAD	80	0
3	66M	–	–	–	18	A-LAD	85	12
4	64M	–	–	–	36	A-Right†	99	20
5	67M	–	+	–	18	Mid-LAD‡	68	43
6	62M	+	–	–	48	A-LAD	71	30
	— —	—	—	—	—	A-Diag.	62	27
	— —	—	+	–	50	A-LAD*	95	27
7	67F	+	+	–	84	P-LAD	73	20
8	60F	+	+	–	6	P, mid, D-LAD	95	10
9	63F	–	+	+	6	D-LAD	90	20
10	57F	–	+	+	5	A-LAD	75	0
	— —	—	—	—	—	P-LAD	62	10
	— —	—	+	–	8	A-LAD*	84	8
11	60M	+	–	–	36	Mid, D-LAD‡	90	0
12	52M	+	+	–	48	A-LAD	75	0
13	48M	–	–	–	3	A-LAD	95	50
14	45F	+	+	–	6	A-LAD	66	16
15	44M	+	+	–	36	A-LAD	95	8
16	70M	–	–	–	24	A-LAD	78	34
				Unsuccessful				
17	55M	–	+	–	48	A-LAD	95	95
18	57M	–	+	+	48	A-Right†	95	100
19	63M	–	–	–	8	A-LAD	100	100
20	52M	–	–	–	4	A-LAD	95	95

*Repeat dilatation for restenosis.
†Right internal mammary graft.
‡Late coronary bypass operation.
A = anastomosis; D = distal; Diag. = diagonal; LAD = left anterior descending artery; MI = myocardial infarction; P = proximal; RCA = right coronary artery; – = absent; + = present; — = not applicable.

hospital myocardial infarction or died. Coronary bypass surgery was performed within 48 hours in 2 patients with unsuccessful angioplasty and persistent symptoms. Percent diameter stenosis before the procedure was significantly higher in lesions with an unsuccessful outcome (96 ± 2 vs 81 ± 11% for successfully treated lesions [p = 0.015]), although lesion morphology was similar in the 2 groups (Table II). During the follow-up period, 16 of the 18 patients (89%) in whom follow-up was available reported symptomatic improvement (Figure 1). Repeat catheterization demonstrated restenosis at the site of angioplasty in 3 patients. Coronary angioplasty was performed in 2 of these patients and repeat bypass surgery was performed in 1. One additional patient with persistent symptoms after successful angioplasty underwent repeat bypass operation without repeat coronary arteriography.

Angioplasty of stenoses within internal mammary bypass grafts is a useful therapeutic alternative in patients with recurrent symptoms after coronary bypass operation.[1–4] In this series of 20 consecutive patients undergoing coronary angioplasty of 24 internal mammary graft

TABLE II Morphology of Lesions Involving the Internal Mammary Artery

	Unsuccessful (n = 4)	Successful (n = 20)
Before procedure		
Length (mm)	17 ± 15	12 ± 12
Eccentric	0 (0)	4 (20)
Diffuse graft disease	2 (50)	4 (20)
Bend ≥45°	0 (0)	6 (30)
Proximal tortuosity	2 (50)	13 (65)
Number of bends ≥90° before lesion	2.2 ± 3.9	2.2 ± 2.6
Luminal irregularity	0 (0)	4 (25)
After procedure		
Minor dissection	0 (0)	3 (15)

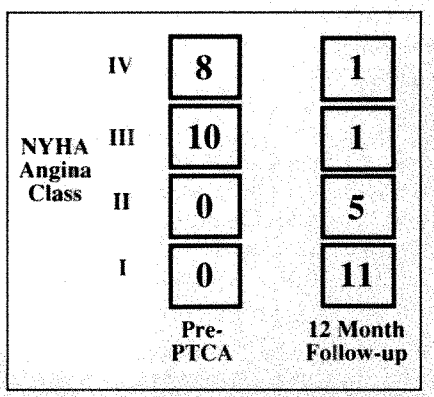


FIGURE 1. New York Heart Association (NYHA) functional classification before percutaneous transluminal coronary angioplasty (Pre-PTCA) and an average of 12 months after coronary angioplasty of internal mammary graft stenoses.

stenoses, a lesion success rate of 83% is reported. Lesions in this series were often long (average length 13 ± 12 mm) and frequently located in vessels with severe proximal tortuosity (63%) or, on occasion, in diffusely diseased arterial grafts (25%). Angioplasty was successfully performed in 2 patients with diffuse stenoses involving the entire extent of the internal mammary graft; sequential balloon inflations along the length of the graft resulted in a marked improvement in its overall dimensions. Percent diameter stenosis before the procedure was higher in unsuccessfully dilated lesions than in lesions with a successful outcome ($p = 0.015$), similar to findings in native vessel coronary angioplasty.[6] Analysis of other pre-procedural lesion morphologic features failed to demonstrate any other significant correlates of an unsuccessful outcome, although all unsuccessful lesion attempts were severe (≥95%), concentric stenoses without apparent luminal irregularities suggestive of thrombus, and all involved the anastomotic site of the internal mammary graft. Failures were attributed to the inability to cross and dilate the anastomotic stenosis rather than to elastic recoil or the development of periprocedural complications.

In the present series, long-term symptom improvement was obtained in 90% of patients 12 months after internal mammary angioplasty (Figure 1). Previous series have reported a similar incidence of late improvement.[1-4] Recurrence of symptoms due to restenosis has been reported in 0 to 31% of successfully treated patients, although angiographic follow-up rates have been extremely low in most series (<25%), and the true incidence of angiographic restenosis is not known.[1-4] Furthermore, an additional 5 to 10% of patients require repeat bypass operation because of incomplete revascularization or progression of multivessel coronary disease.[1-4] In the present series, 2 patients developed restenosis at 2 and 3 months after angioplasty, both successfully treated with repeat dilatation. Two patients underwent coronary bypass operation due to recurrent or persistent symptoms attributed to multivessel coronary artery disease.

The present series has several limitations. First, the small number of lesions with an unsuccessful outcome limits the overall power to detect small differences in the identified clinical and angiographic subsets. Second, as in prior series,[1-4] angiographic follow-up was obtained only in patients with recurrent symptoms. As a result, the incidence of angiographic restenosis was not evaluated. Finally, all patients in the present series had multivessel coronary artery disease; subsequent revascularization may have been dictated by persistent or recurrent symptoms of concomitant coronary disease not directly related to recurrence of the internal mammary artery stenosis.

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Value of Ventilation/Perfusion Scans Versus Perfusion Scans Alone in Acute Pulmonary Embolism

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The value of ventilation/perfusion (V/Q) lung scans in the diagnosis of acute pulmonary embolism (PE) was described in the results of the collaborative study of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED).[1] The effects of preexisting cardiac or pulmonary disease and of a normal chest radiograph on the diagnostic value of V/Q scans[2,3] were also described among patients in PIOPED. The present report assesses the value of V/Q scans compared with that of perfusion scans alone in the diagnosis of acute PE.

Patients reported in this investigation participated in the collaborative study of PIOPED. Patients were randomly assigned to 2 groups. The first group consisted of patients selected for obligatory pulmonary angiography, providing that their V/Q scans were abnormal. Patients in this group were included in the PIOPED report of the value of V/Q scans in acute PE.[1] The second group included patients who underwent angiography only at the request of their attending physicians based on clinical circumstances. These patients were not included in the original PIOPED report. The present investigation includes data collected from both groups of patients in PIOPED.

Ninety-eight patients with suspected acute PE were randomly selected to have perfusion scans read independently of, as well as in combination with, the ventilation scans. These lung scans were read without knowledge of the clinical manifestations or results of the pulmonary angiograms. PE was diagnosed by pulmonary angiography in 29 of these patients. PE was excluded by angiography in 33 patients and by outcome committee classifi-

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TABLE I Patient Characteristics

	V/Q and Perfusion Evaluation (n = 98)	V/Q Evaluation (n = 1,389)
Age (yr)	56 ± 18	55 ± 17
Men	48 (49%)	627 (45%)
Hospital service		
Medical/CCU	46 (47%)	532 (38%)
Surgical	18 (18%)	252 (18%)
Outpatient	4 (4%)	58 (4%)
Emergency room	19 (19%)	390 (28%)
Intensive care unit	10 (10%)	141 (10%)
Other	1 (1%)	16 (1%)
Hospital mortality	7 (7%)	60 (4%)
Associated diagnoses		
COPD	11 (11%)	180 (13%)
Asthma	7 (7%)	118 (8%)
Pneumonia	4 (4%)	99 (7%)
ARDS	0 (0%)	3 (0.2%)
Myocardial infarction	12 (12%)	187 (13%)
Coronary heart disease	24 (24%)	287 (21%)
PaO_2 (mm Hg)	67 ± 16 (n = 81)	70 ± 17 (n = 1,021)
PA mean pressure (mm Hg)	24 ± 11 (n = 65)	23 ± 10 (n = 1,014)

Continuous variables are reported as mean ± SD. No differences between groups were statistically significant.
ARDS = acute respiratory distress syndrome; CCU = coronary care unit; COPD = chronic obstructive pulmonary disease; PA = pulmonary artery; PaO_2 = partial pressure of oxygen in arterial blood; V/Q = ventilation/perfusion.

TABLE II Pulmonary Embolism Among 67 Patients with Various Probability Ventilation/Perfusion Scans and Perfusion Scans Alone

Interpretation (probability of PE)	V/Q Scan, +PE/No. of Pts. (%)	Perfusion Scan, +PE/ No. of Pts. (%)
High	15/16 (94)	14/15 (93)
Intermediate	9/25 (36)	14/38 (37)
Low	5/25 (20)	0/12 (0)
Near normal/normal	0/1 (0)	1/2 (50)

All differences between ventilation/perfusion (V/Q) scans and perfusion scans alone were not significant.
PE = pulmonary embolism.

TABLE III Lung Scan Interpretations in 98 Patients with Ventilation/Perfusion Scans and Perfusion Scans Alone

Interpretation (probability of PE)	V/Q Scan (%)	Perfusion Scan (%)
High	18 (18)	17 (17)
Intermediate	34 (35)	48 (49)
Low	37 (38)	23 (23)*
Near normal/normal	9 (9)	10 (10)

*$p < 0.05$
Abbreviations as in Table II.

cation in 5. The diagnosis was uncertain (angiogram or outcome classification not performed) in 31 patients. Therefore, the diagnosis of PE was established in 67 patients, and the diagnostic validity of V/Q scans compared with that of perfusion scans alone was evaluated in these patients. Comparisons of the frequency of various scan interpretations (high probability, intermediate probability, low probability, and near normal/normal scans) were obtained in all 98 patients. Criteria for the diagnosis of PE by angiography were the identification of an embolus obstructing a vessel, or the outline of an embolus (filling defect) within a vessel. Methods of pulmonary angiography and of outcome classification were previously described.[1]

Methods of obtaining and interpreting V/Q scans were previously described.[1] *Perfusion scans alone were read according to the same criteria as V/Q scans, except the location of perfusion defects was related only to the location of abnormalities on the plain chest radiograph. Perfusion scans were read by radiologists at centers other than the one at which the V/Q scan was read.*

Comparisons of the characteristics of the 98 patients randomly selected for comparisons of perfusion with V/Q scans were made with those of the 1,389 patients who were not randomly evaluated by both V/Q scans and perfusion scans alone.

A chi-square test with Yates' correction was used to compare the prevalence and distributions of clinical features, and to compare the predictive value, and individual sensitivities and specificities of V/Q scans. Positive predictive value was defined as the percentage of patients with an abnormal V/Q scan who had PE. Sensitivity was defined as the proportion of cases of PE correctly diagnosed. Specificity was defined as the proportion of negative tests among patients in whom PE was absent. Comparisons of continuous variable means were performed with Student's t test. All results are based on computations performed at the Henry Ford Heart and Vascular Institute using a data tape provided by the PIOPED data and coordinating center.

The characteristics of the 98 patients randomly selected for analysis of their perfusion scans alone (in addition to their V/Q scans) were compared with those of the remaining patients who were not selected for comparative analyses (Table I). No characteristic showed a statistically significant difference between the groups.

The positive predictive value of high-probability V/Q scans was 15 of 16 (94%), which did not differ significantly from that of high-probability perfusion scans (14 of 15 [93%]) (Table II). The frequency of PE among patients with low-probability V/Q scans (5 of 25 [20%]) did not differ significantly from that of low-probability perfusion scans alone (0 of 12 [0%]; p = not significant [NS]). Few patients had nearly normal/normal V/Q or perfusion scans.

More patients who had V/Q scans had low-probability interpretations than did those with perfusion scans alone (37 of 98 [38%] vs 23 of 98 [23%]; $p < 0.05$) (Table III). The frequency of high- or intermediate-probability, or near normal/normal lung scans was similar among V/Q scans and perfusion scans alone (p = NS).

The sensitivity of high-probability V/Q scans (15 of 29 [52%]) did not differ from that of high-probability perfusion scans (14 of 29 [48%]; p = NS). The specificity of high-probability V/Q scans (37 of 38 [97%]) was identical to that of high-probability perfusion scans (37 of 38 [97%]).

Ventilation scans were obtained in combination with perfusion scans with the thought that ventilation would be abnormal in areas of pneumonia or local hypoventilation, but would be normal in PE.[4] The present study

indicates that a high-probability perfusion scan has no less diagnostic validity in acute PE than does a high-probability V/Q scan. Similarly, a low-probability or near normal/normal perfusion scan excluded PE with no less validity than did a low-probability or near normal/normal V/Q scan. Somewhat more patients who had only perfusion scans had intermediate (indeterminate) probability readings than did those with V/Q scans, but this difference was not statistically significant. Therefore, the data indicate that if ventilation scans cannot be performed, reliable information can be obtained if the interpretation of the perfusion is high or low probability, or near normal/normal. If the perfusion scan is interpreted as intermediate probability for PE, a subsequent VQ scan may change the interpretation to a more definitive probability.

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Comparison of Procedural Results and Risks of Coronary Angioplasty in Men and Women for Conditions Other Than Acute Myocardial Infarction

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Cardiovascular disease is the leading cause of death in women. Early reports of the results of coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA) in women[1,2] suggested increased procedural risks compared with those in men, which may have, in part, led to a reluctance to offer revascularization procedures to women with coronary heart disease.[3] More recent experiences indicate that the intrinsic risk of both CABG and PTCA in women may be no greater than in men.[4,5] To further evaluate the risk and results of PTCA in women compared with in men, we examined the influence of gender on the procedural results in a large cohort of patients treated with PTCA.

The clinical features and procedural results from our initial 10,000 PTCA procedures were prospectively entered in a computer database. The 9,175 patients treated with PTCA for indications other than acute myocardial infarction were considered for analysis in this study. Successful dilatation of a narrowing was defined as a reduction in diameter stenosis after PTCA to ≤40% in multiple views by visual assessment. Procedural death was defined as any death before hospital discharge. Procedural infarction was defined by the development of Q waves on electrocardiography after PTCA.

Results and complications were compared in men and women using Student's t *test for continuous variables, and Fisher's exact test for categorical variables. Stepwise logistic regression analysis was used to examine independent predictors of in-hospital death. Factors analyzed included gender, age, prior CABG, left ventricular function, left main coronary artery narrowing and equivalent anatomy, number of diseased vessels with ≥70% diameter stenosis, New York Heart Association angina classification and presence of prior myocardial infarction. The multivariate odds ratio was calculated as the natural algorithm of the regression coefficient and reflected the independent risk of death associated with the presence of a specific variable when all other variables were held constant. Data are mean ± SD. A p value <0.05 was considered significant.*

In all, 9,175 PTCA procedures were analyzed. Table I compares clinical features between the 7,142 men and 2,033 women treated with PTCA. Women were older, and more frequently had class IV angina and diabetes mellitus. Fewer women had 3-vessel disease, prior CABG or left main narrowing.

A comparison of the procedural results and complications in men and women is shown in Table II. Death was more frequent in women, whereas the rates of myocardial infarction and emergency CABG were comparable.

Multivariate analysis of independent predictors of in-hospital death after PTCA identified (in descending order of importance) the number of coronary arteries with ≥70% narrowing, left ventricular ejection fraction, absence of prior CABG, New York Heart Association class IV angina and age. After adjustment for the increased age and anginal symptoms of women, PTCA in women was not identified as an independent predictor of

TABLE I Comparison of Clinical and Angiographic Features in Men and Women Treated with Percutaneous Transluminal Coronary Angioplasty

	Men	Women	p Value
No. of pts.	7,142	2,033	
Age (yr)	59 ± 10	64 ± 10	<0.001
Prior bypass surgery (%)	1,788 (25)	350 (17)	<0.001
Diabetes mellitus (%)	865 (12)	474 (23)	<0.001
NYHA angina class IV (%)	2,548 (36)	1,084 (53)	<0.001
Ejection fraction ≤0.40 (%)	693 (10)	188 (9)	0.5
Left main coronary narrowing (%)	156 (2)	23 (1)	0.002
3-vessel coronary narrowing (%)	2,660 (37)	609 (30)	<0.001

NYHA = New York Heart Association.

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TABLE II Comparison of Procedural Results and Complications in Men and Women Treated with Percutaneous Transluminal Coronary Angioplasty

	Men	Women	p Value
No. of pts.	7,142	2,033	
Narrowings treated	17,361	4,517	
Successful PTCA of narrowing (%)	16,451 (95)	4,273 (95)	0.8
Multivessel PTCA (%)	3,063 (43)	796 (39)	0.01
Emergency bypass surgery (%)	117 (1.6)	32 (1.6)	0.8
Procedural infarction (%)	98 (1.4)	34 (1.7)	0.3
Hospital death (%)	57 (0.8)	29 (1.4)	0.01
Any major complication (%)	232 (3.2)	75 (3.7)	0.3

PTCA = percutaneous transluminal coronary angioplasty.

TABLE III Multivariate Odds Ratio of Variables Independently Predictive of In-Hospital Death After Percutaneous Transluminal Coronary Angioplasty in 9,175 Patients

Variable	Odds Ratio
3-vessel coronary narrowing	18
2-vessel coronary narrowing	5
Ejection fraction ≤ 0.40	4
No prior bypass surgery	4
NYHA angina class IV	3
Age ≥ 70 years	2

NYHA = New York Heart Association.

in-hospital mortality. The multivariate odds ratios are shown in Table III.

Our results from a large experience with PTCA show that women are more likely than men to die in-hospital after PTCA, but that this difference disappears after adjusting for potential confounding clinical and angiographic variables. This observation has important implications for the care of women with coronary artery disease. The initial multicenter report examining gender related differences with PTCA performed from 1977 to 1981 reported lower success and higher in-hospital mortality when PTCA was performed in women.[2] In an updated analysis of predictors of procedural mortality for PTCA performed in the years 1985 to 1986, female gender was again identified as an independent predictor of death,[6] and it was suggested that female gender be one of the variables used to weigh the decision whether to perform PTCA.

Evidence for potential underuse of therapeutic procedures in women hospitalized for coronary heart disease was recently identified.[3] Data from >80,000 hospital discharges in 1987 indicated that women with any form of coronary heart disease were significantly less likely than men to undergo coronary angiography and myocardial revascularization. These data remained significant even when only patients with acute myocardial infarction were analyzed.[3] Our data showing that female gender is not independently predictive of procedural mortality, together with the favorable results of PTCA in women found by McEniery et al,[5] suggest that PTCA should not be withheld in women who are thought to be appropriate anatomic candidates for fear of reduced success or increased major complications. Whether identification of women with coronary heart disease earlier in their course may improve the procedural outcome with PTCA (as has been suggested with CABG)[4] remains to be determined.

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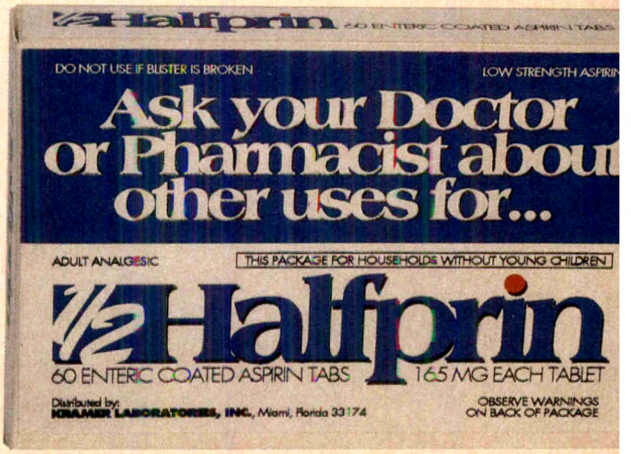
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Usefulness of Silent Subendocardial Ischemia Detected by ST-Segment Depression in Postmyocardial Infarction Patients as a Predictor of Ventricular Arrhythmias

Ana Maria Camacho, MD, Josep Guindo, MD, and Antonio Bayés-de-Luna, MD

There is conclusive experimental and clinical evidence that severe, transmural and persistent acute ischemia (silent or symptomatic), the maximum exponent of which is myocardial infarction, can trigger malignant ventricular arrhythmias and sudden cardiac death.[1] Furthermore, a relation between severe acute transmural but transient ischemia appearing during Prinzmetal's angina[2] or during percutaneous transluminal angioplasty[3] and ventricular arrhythmias is well known, although such arrhythmias are rarely malignant. However, the relation between ventricular arrhythmias and subendocardial ischemia (silent or symptomatic) has only been partially studied, and results are contradictory.[4-7]

To determine whether there is a clear relation between episodes of silent myocardial ischemia detected by Holter electrocardiography and ventricular arrhythmias, we prospectively studied 70 consecutive postmyocardial infarction patients (65 men and 5 women, aged <75 years, mean 54 ± 10). The infarction involved the anterior wall in 28 cases (40%), inferior wall in 38 (54%) and was non-Q-wave in 4 (6%). No patient had other associated heart disease. No patient was an insulin-dependent diabetic, nor did any have arterial hypertension or other disease-producing alterations in the ST segment on baseline electrocardiogram.

Ten to 20 days after the acute phase of myocardial infarction, all patients in the study underwent Holter electrocardiography (24 to 48 hours of recording) (Nihon-Kohden 3-channel model, DMC-3000K, Tokyo, Japan), exercise testing (modified Bruce protocol) and isotopic ventriculography (Gammacamera GE-Maxi connected in line with a digital Gamma-11; images were obtained after in vivo red blood cell labeling with 20 mCi of technetium-99m; each cardiac cycle comprised 21 frames of 740,000 counts each). During Holter electrocardiography, episodes of evident silent myocardial ischemia were defined as those producing ST-segment depression ≥1 mm, lasting >1 minute, and with an interval of 1 minute between episodes. For each episode, we also studied periods of 5 minutes before and after ST-segment depression, and considered these to be periods of probable silent ischemia. We wanted to determine whether the incidence of ventricular arrhythmias during these periods is greater than that during control periods (without ischemia). Global silent ischemia was defined as the sum of evident and probable silent ischemia.

Of the 70 postmyocardial patients studied, 21 presented with silent myocardial ischemia by Holter electrocardiography (30%). In all, we recorded 113 episodes of ST-segment depression: 110 (97.3%) were silent, and only 3 (2.7%) (all occurring in 1 patient) were symptomatic. During 643 hours and 54 minutes of Holter monitoring, we recorded 601 hours and 20 minutes without ischemia, 24 hours and 18 minutes of evident silent ischemia, and 18 hours and 10 minutes of probable silent ischemia (42 hours and 28 minutes of global silent ischemia).

The duration of 110 episodes of silent myocardial ischemia ranged between 1 and 51 minutes (mean 11.9 ± 9.4). ST-segment depression ranged from 1 to 2.5 mm (mean 1.2 ± 2.4). Ventricular premature complexes appeared in 19 of the 110 events (17.2%). Table I shows the incidence of ventricular arrhythmias during periods of evident, probable and global ischemia, and without ischemia. There were no significant differences between groups. Furthermore, we found no statistically significant differences between episodes with and without ventricular arrhythmias regarding duration of events, heart rate and ST-segment depression. Although ventricular premature complexes were more frequent in patients with (309 ± 776/24 hours) than in those without (116 ± 313/24 hours) silent myocardial ischemia, differences were not statistically significant. The percentage of patients with frequent ventricular premature complexes

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TABLE I Relation Between Silent Myocardial Ischemia and Ventricular Arrhythmias in Holter Monitoring

Silent Ischemia	Time	VPC	Couplets and Runs
Absent	601 hours, 20 minutes	6,400 = 10.64 × hour	48 = 0.07 × hour
Present	24 hours, 18 minutes	176 = 7.33 × hour	2 = 0.08 × hour
Probable	18 hours, 10 minutes	339 = 18.80 × hour	2 = 0.11 × hour
Global	42 hours, 28 minutes	515 = 12.20 × hour	4 = 0.10 × hour

VPC = ventricular premature complexes.

(≥10/hour) or complex ventricular arrhythmias (pairs or salvos) was similar in both groups.

Twenty-eight patients presented with ST-segment depression ≥1 mm during exercise testing. Mean ST-segment depression was 1.8 mm (range 1 to 3.5 mm). In 11 patients, ST deviation was accompanied by angina. Ventricular arrhythmias were present in 13 patients (19%); 7 of 42 (17%) without ST-segment depression, 2 of 11 (18%) with angina and ST-segment depression, and 4 of 17 (24%) with ST-segment depression without angina (p = not significant). The mean ejection fraction for all patients was 43%, and no differences were observed between those with and without ischemia, or those with silent and symptomatic ischemia.

There are contradictory results regarding the association of silent ischemia and ventricular arrhythmias in patients with stable coronary artery disease. Although a relation between the 2 was reported in studies by Stern et al[4] and Carboni et al,[5] studies by Hausmann et al[6] and Graboys et al[7] appear to indicate the contrary. In patients with malignant ventricular arrhythmias, Gomes et al[8] and Bayés de Luna et al[9] were not able to demonstrate that silent ischemia had an important role in triggering such arrhythmias. However, ST-segment alterations suggestive of myocardial ischemia have been found in approximately one third of patients who died suddenly while undergoing Holter monitoring.[9,10] Our study differs from those published to date in that all our patients had a recent myocardial infarction with a moderately depressed ventricular function (mean ejection fraction 43%).

We conclude that in this selected group of postmyocardial infarction patients with moderate left ventricular dysfunction, silent subendocardial ischemia (defined as ST-segment depression between 1 and 2.5 mm) is not accompanied by an increase in ventricular arrhythmias. However, the high-density ventricular arrhythmias during nonischemic periods suggest that postinfarction patients have a global mechanism for arrhythmias, which may mask the relation of silent ischemia to arrhythmias. It remains unclear whether more severe subendocardial ischemia is associated with ventricular arrhythmias. As with Prinzmetal angina,[2] in which a clear association between the degree of ST elevation and ventricular arrhythmias has been demonstrated, a correlation between the degree of ST depression and the incidence of ventricular arrhythmias may be possible in subendocardial ischemia. Further studies should be performed to investigate this possibility.

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Operational Definition of Normal Sinus Heart Rate

David H. Spodick, MD, DSc, Padma Raju, MD, Richard L. Bishop, MD, and Robert D. Rifkin, MD

Heart rate (HR) is an accurately measurable descriptor of patients' status immediately available to physicians without special instrumentation. Accepted limits of HR have long been set at 60 and 100 beats/min for normal sinus rhythm. Experience suggests that both these traditional limits are too high, except under undue autonomic activation, an imposed abnormality. In practice, this translates into suspicion of abnormality when a patient has a resting HR between 90 and 100 beats/min, rather than a rigidly classified "tachycardia" at ≥100 beats/min. Furthermore, with the current emphasis on fitness we are not unduly concerned with the asymptomatic patient with a resting HR between 50 and 60 beats/min. Whereas 1 distinguished investigator reported the traditional limits of 60 and 100 beats/min as "generally agreed"[1] (and they are indeed long-established New York Heart Association recommendations),[2] a search of previous publications revealed no investigations that systematically define sinus tachycardia and bradycardia for clinical application. We reexamined the question of operational definitions for sinus bradycardia and tachycardia. Our investigation was designed to determine if a clinically normal population suggested other limits, compare them with the literature and, if comparable, redefine sinus tachycardia and bradycardia.

We reviewed the data of 500 consecutive asymptomatic men and women (aged 50 to 80 years) who attended a screening clinic and had no history or clinical findings consistent with diseases of the heart, cardiovascular system or other systems. History included detailed statements of any significant illness beyond mild respiratory infections and equivalent conditions, any symptoms of cardiac, pulmonary or other disease, and particularly attacks of paroxysmal abnormal heart action and regular or current use of medications (except occasional symptomatic treatments). Detailed physical examinations were negative for all systems. Laboratory studies included standard chest x-ray, electrocardiogram, urine analysis, and complete blood count and glucose.

HR was measured from electrocardiograms recorded between 1 and 5 P.M. The relation between HR and age was analyzed by linear regression. Confidence limits and significance testing of the correlation coefficients was performed using Fisher's Z transformation: $Z = 1/2Ln(1 + rho)/(1 - rho)$, where rho is the correlation coefficient.[3]

These normal subjects included 367 women and 123 men. The breakdown by sex, age and HR (rounded means, SD and 95% confidence intervals) is shown in Table I. For this sample, mean HR by quinquennium was within the narrow range of 67 to 76 beats/min, with fairly wide SD for each subgroup. For the entire sample, mean HR was 69 and 73 beats/min for men and women, respectively.

Linear regression of HR against age in women yielded: HR = (0.095 × age) + 67.34, correlation coefficient 0.063 (95% confidence limits −0.04 to 0.164; SEE 11.22). In men, HR = (−0.02 × age) + 70.87, correlation coefficient 0.014 (95% confidence limits −0.16 to 0.191; SEE 12). Thus, there was no clinically important dependence of HR on age, nor was any statistically significant relation between these variables detected, despite the large sample sizes. Two SD yields rounded extremes of 46 and 93 beats/min for men, and 51 and 95 beats/min for women.

Our clinical impression that traditional HR limits (unsupported except by general acceptance)[1] are nonoptimal agrees with the results of this study, indicating extremes of 46 and 95 beats/min to be more realistic than the traditional 60 to 100 beats/min for resting normal sinus HR. For practical purposes, rounded thresholds of 50 and 90 beats/min should alert the clinician to HR abnormality. Furthermore, the results are remarkably similar to the reported resting HR in very large normal series. The Framingham Heart Study participants with-

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TABLE I Heart Rates by Gender and Age (n = 500)*

Age (yr)	Men			Women		
	No. of Pts.	HR (beats/min)	95% CI	No. of Pts.	HR (beats/min)	95% CI
50–54	13	75 ± 15	45–105	57	71 ± 10	52–90
55–59	40	67 ± 10	47–87	111	74 ± 10	53–94
60–64	21	70 ± 13	45–96	88	73 ± 11	52–94
65–69	23	67 ± 10	48–87	47	72 ± 13	47–98
70–74	19	71 ± 13	47–96	43	76 ± 11	54–98
75–80	7	71 ± 14	43–99	21	73 ± 12	50–96
Total	123	69 ± 12	43–93	367	73 ± 11	52–94

*All numbers rounded.
CI = confidence intervals; HR = heart rate.

out demonstrable disease in age deciles 35 to 44 through 75 to 84 years had a mean HR of 74 to 76 beats/min, with a slight to absent age trend.[4] In that study, overall and cardiovascular mortality rates increased progressively with resting HR, with no indication of critical values or thresholds. (In this connection, 1-year mortality after myocardial infarction correlated with numerous factors, but only HR was independently predictive on multivariate analysis, especially at >90 beats/min[5] [i.e., a flat trend from <50 to 70 beats/min, then increased progressively, particularly when >90 beats/min].)

HR greater than the convenient traditional tachycardia threshold of 100 beats/min tends to alarm the physician in asymptomatic as well as symptomatic patients and needs further investigation. But is 100 beats/min a realistic threshold? That tachycardia (however defined) should raise a red flag is seen in the consistent relation of cardiovascular death to resting HR in both sexes and at all ages.[4,6–10] These subjects may have had relative or absolute resting tachycardias (depending on definition) related to poor physical fitness, subclinical reduction of cardiac reserve due to decreased myocardial function,[4,11] inappropriate sensitivity to autonomic factors, or a hyperbeta-adrenergic state.[12–15] Furthermore, the latter may also signify acute or chronic cardiac or noncardiac disease, which the clinician would investigate. Our results suggest a lower threshold for such investigation. Similarly, bradycardia (particularly in the elderly who are not physically fit) may need further evaluation (e.g., for sinoatrial node dysfunction if patients are symptomatic), and our data again indicate a lower HR threshold.

The results of this study suggest a new consensus: 45 and 95 beats/min to define the extremes of normal sinus HR. For operational simplicity (because so many of the subjects had HR between 50 and 90 beats/min), perhaps when HR alone alerts the clinician, these thresholds should be >90 and <50 beats/min to improve the sensitivity of the tachycardia threshold, and the specificity of the bradycardia threshold.

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Location of Accessory Tracts in Concealed Preexcitation by Atrial Phase Analysis of Radionuclide Ventriculography During Induced Supraventricular Tachycardia

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Radionuclide phase analysis may be used to assess cardiac function, regional wall motion and conduction abnormalities.[1-3] The purpose of this research was to evaluate ventricular and especially atrial phase analysis to demonstrate abnormal conduction during induced supraventricular tachycardia in patients with concealed tracts.

After giving informed consent, 20 subjects (12 women and 8 men, mean age 40 years, range 17 to 67) with supraventricular tachycardia underwent physical examination, electrocardiography, echocardiography and electrophysiologic study. If the latter confirmed retrograde conduction by an accessory tract during tachycardia, patients were considered for gated radionuclide ventriculography. This test was performed using labeled red blood cells with 25 to 30 mCi of technetium-99m, a gamma camera and computer (Ohio Nuclear 410 Sigma, Technicare, Ohio, and Digital PDP 11/34, DEC, Massachusetts) in the left anterior oblique view at baseline and during induced tachycardia. Biventricular ejection fraction and initial harmonic phase analysis were then obtained, using Student and Wilcoxon tests to compare mean values.

Physical examination, electrocardiography and echocardiography were normal in all cases. Electrophysiologic study revealed a concealed tract located laterally in the left ventricle in 15 subjects, and along the septum in 5. Heart rates were 84 ± 21 beats/min at baseline, and 186 ± 23 beats/min during tachycardia ($p < 0.00001$). Right ventricular ejection fractions were 54 ± 6% at baseline, and 41 ± 8% during tachycardia ($p < 0.00001$); left ejection fractions were 69 ± 8% and 60 ± 11%, respectively ($p < 0.0001$). In the entire group, atrial images at baseline revealed an earlier emptying in the left atrium, with phase angle values significantly lower than in the right atrium (184 ± 11° vs 173 ± 16°; $p = 0.0016$). These values are similar to those of our normal subjects.[4] In the right and left ventricles, mean phase values were not significantly different (−9.2 ± 6° and −8.6 ± 5°, respectively). Earlier left ventricular emptying in the left lateral tracts of 4 of 15 subjects (27%) suggested preexcitation.

During tachycardia in patients with left lateral tracts, phase images showed striking asymmetric atrial emptying in the left atrium in synchrony with that of ventricles in 14 of 15 cases (93%). Mean phase angle values between both atria during tachycardia were significantly different from those at baseline, being much lower in the left atrium (Figure 1). In 1 patient, the images were not different from those at baseline. In the 5 cases with concealed septal tracts, phase images disclosed both right and left atrial emptying in synchrony with ventricles in 1, earlier left atrium phase in 1, and similar images to those at baseline in the remaining 3 cases. No significant difference between right and left atrial phase angle values was found in the subjects (Figure 2). In ventricles, there was no significant difference between left and right chambers in lateral or septal tracts (Figures 1 and 2).

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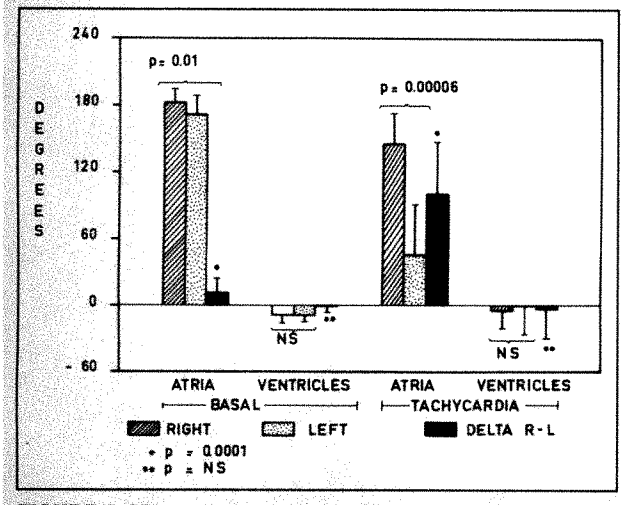


FIGURE 1. Mean phase angle values in basal and tachycardia studies in each cardiac chamber in 15 cases with left lateral concealed tracts. Delta R-L = mean of right minus left cavity; NS = not significant.

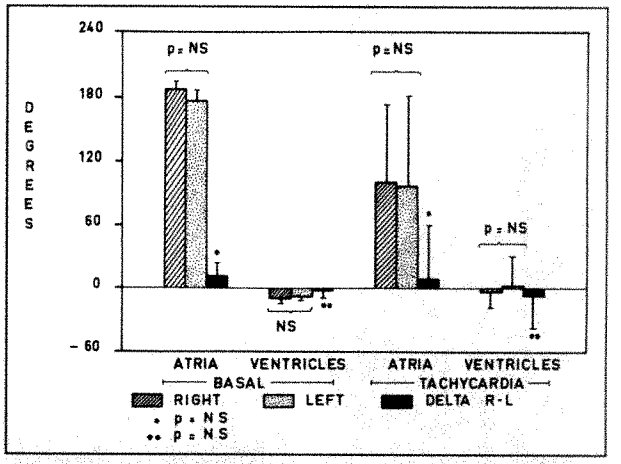


FIGURE 2. Mean phase angle values in basal and tachycardia studies in each cardiac chamber in 5 cases with septal concealed tracts. Abbreviations as in Figure 1.

Phase analysis of resting radionuclide ventriculography has been used to locate accessory tracts in patients with preexcitation syndromes.[2] Ventricular phase shifts can be assessed owing to the fact that tract conduction is anterograde. In concealed pathways, studies can frequently be normal.[5] In our results, only 27% of patients had abnormal resting ventricular phase analysis, compatible with preexcitation and not detected by electrocardiography. This sensitivity was expected to be lower than that in nonconcealed tracts that have abnormal basal electrocardiograms.[2] Furthermore, it was demonstrated that phase images during tachycardia at the atrial level detected earlier left chamber emptying (in synchrony with the ventricles) in 93% of cases where the bypass was in the lateral aspect of the left ventricle, in relation to retrograde ventriculoatrial conduction.[6] However, results were less encouraging in septal tracts, with only 1 of 5 cases showing simultaneous earlier emptying of both atria, a pattern that could be considered compatible with a pathway in the septum. With regard to ventricular function, there was a significant decrease in ejection fraction during supraventricular tachycardia, in agreement with previous data in patients with cardiac pathology or very rapid heart rate.[3] Atrial systole out of synchrony with the opening of the atrioventricular valves, as well as the shorter diastolic period, can explain the lower ejection fraction.

It is concluded that phase analysis can demonstrate retrograde ventriculoatrial conduction with excellent sensitivity in concealed left lateral tracts, if atrial (rather than ventricular) emptying is assessed during tachycardia. This method could be used in some cases when electrocardiography is not conclusive or when electrophysiologic study (the gold standard technique) cannot be performed, but less invasive esophageal stimulation is possible. Atrial phase analysis may also be improved in the future, if used in conjunction with single-photon emission computed tomography.

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Initial Results of Peripheral Vascular Angioplasty Performed by Experienced Interventional Cardiologists

Christopher J. White, MD, Stephen R. Ramee, MD, Tyrone J. Collins, MD, C. Daniel Procter, MD, and Larry H. Hollier, MD

Percutaneous transluminal angioplasty has become the procedure of choice for the treatment of selected patients with peripheral vascular occlusive disease. Since its first description in 1964,[1] and the development of inflatable balloon catheters to dilate lesions in 1974,[2] the technique has gained wide acceptance and been performed primarily by interventional radiologists. However, nonradiologists including cardiologists, and vascular surgeons and internists who are primarily involved in the care and treatment of patients with atherosclerotic vascular disease have begun to perform this procedure. This has generated debate regarding the necessary qualifications for certification and credentialing of physicians to perform peripheral angioplasty. Recently, suggestions for training standards were published in an attempt to ensure that high-quality peripheral angioplasty is practiced.[3,4] This study reports the immediate procedural outcomes of a consecutive series of patients treated with percutaneous techniques, which represent the initial peripheral angioplasty results of experienced interventional cardiologists working in collaboration with vascular surgeons.

Each primary operator (CJW, SRR, TJC) was a board-certified interventional cardiologist with a minimum of 3 years experience performing coronary angioplasty after fellowship training. Each operator had performed >500 coronary angioplasty procedures as the primary operator, and was experienced in performing diagnostic aortography and renal artery angiography. In preparation for beginning peripheral angioplasty, we attended peripheral angioplasty demonstration courses, observed cases performed in a busy peripheral interventional laboratory, and a recognized expert in peripheral vascular angioplasty was present in our laboratory as a proctor for the initial 5 cases. For continuing education, we participate in a weekly vascular surgery teaching conference where case selection, results and complications are reviewed.

Patients were selected on the basis of anatomy and symptomatology. The 164 patients and 208 vessels included in this report represent a consecutive series of patients treated over 20 months (November 1988 to June 1990) and are our initial experience. Lower extremity angioplasty was performed in 116 patients for symptoms of ≤2 block claudication (n = 24), ≤1 block claudication (n = 63), or rest pain or threatened limb loss, or both (n = 29). On the basis of either arm claudication (n = 2) or inadequate dialysis flow (n = 28), 30 patients were selected for upper extremity angioplasty. Renal artery angioplasty (n = 18) was performed for both hypertension and renal insufficiency (n = 14), uncontrolled hypertension alone (n = 2) or renal insufficiency alone (n = 2).

We routinely administered 3,000 to 5,000 units of heparin at the beginning of the procedure. We did not routinely anticoagulate patients after percutaneous transluminal angioplasty procedure, unless there was evidence of intravascular thrombus present by angiography. Angiography of the target lesion was performed before and after completion of the angioplasty procedure using standard cardiac catheterization cineangiographic equipment. A successful procedure was defined as the angiographic reduction of the luminal diameter stenosis to ≤20% compared with the nearest normal segment of the dilated vessel.[5]

Successful percutaneous transluminal angioplasty was obtained in 191 of 208 vessels (92%). In the 191 successful procedures, percent luminal narrowing of the stenoses was reduced from 91.9 ± 10.6% to 17.8 ± 11.8% (p <0.001). Angiographic success was obtained in 155 of 157 stenoses (99%) vs 36 of 51 total occlusions (71%) (p <0.01). For successful percutaneous transluminal angioplasty procedures, the lesion length was 4.9 ± 6.7 cm (range 1 to 40) compared with 14.2 ± 11.6 cm (range 1 to 36) for unsuccessful attempts (p <0.01). For lesions ≤3 cm in length, successful percutaneous transluminal angioplasty was obtained in 125 of 126 vessels (99%) vs 66 of 82 (80%) with lesions >3 cm (p <0.01). In patients undergoing lower extremity percutaneous transluminal angioplasty, the baseline ankle brachial index increased from 0.56 ± 0.23 to 0.87 ± 0.19 (p <0.01) after angiographically successful percutaneous transluminal angioplasty.

We did not reduce the luminal diameter narrowing to ≤20% in 17 of 209 vessels (8.1%). Most unsuccessful attempts (15 of 17; 88%) occurred in total occlusions, with 2 occurring in stenotic lesions (residual stenosis >20%) (1 in a dialysis fistula, and 1 in a lower extremity bypass graft). In no patient did an unsuccessful attempt result in worsening of the clinical condition or in the need for emergency surgery.

In all, 7 major complications (4.3%) occurred in 6 patients. There were 5 major groin complications at the site of vascular access, including 3 large hematomas (>5 cm diameter) and 2 femoral artery pseudoaneurysms. One patient with a large femoral hematoma needed a 2-unit transfusion of packed red cells, and 1 treated with adjunctive thrombolysis and balloon dilation of a totally occluded femoral popliteal synthetic bypass graft had

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distal embolization of thrombus, which resolved with continued lytic therapy. No complications resulted in emergency surgery, amputation, myocardial infarction, stroke or death. Minor complications included 4 vascular perforations that occurred during thermal laser angioplasty procedures in totally occluded superficial femoral arteries and were without adverse sequelae.

Our initial experience supports the hypothesis that experienced interventional cardiologists working closely with vascular surgeons have the necessary technical skills to perform peripheral vascular angioplasty in a safe and effective manner. The expertise of our vascular surgery colleagues was relied on for guidance in patient and lesion selection, which contributed to our high rate of success, and low incidence of complications. The results do not demonstrate a learning curve, although early in our experience our case selection was certainly biased toward technically less challenging lesions. However, the percentage of patients with totally occluded vessels (25%), and the average lesion length (5.8 ± 8.0 cm) attest to the relatively difficult lesions we routinely accepted for treatment.

The overall angiographic success rate of 92% for all lesions, and the 99% success rate for percutaneous transluminal angioplasty of stenoses suggests that coronary angioplasty skills can be effectively adapted to the treatment of noncoronary lesions. The data are consistent with those of other investigators in that our success rates were higher for non-total occlusions and lesions of shorter length.[6,7] The overall major complication rate of 4.3% (7 of 164) compares favorably with that of other studies published in the literature.[8,9]

Our experience included upper extremity arterial and venous lesions, hemodialysis access grafts, renal artery stenoses and lower extremity arterial disease, which we approached with a variety of angioplasty devices and techniques. One advantage of applying interventional coronary techniques to peripheral angioplasty was the concept of using guiding catheters for renal artery angioplasty. Conventional renal artery angioplasty does not use a guiding catheter. We reasoned that the renal artery ostium was analogous to a coronary artery ostium. The use of a guiding catheter gives the operator more control during renal artery percutaneous transluminal angioplasty, allowing contrast visualization and translesional pressure gradient monitoring during the procedure.[10]

It has been our experience that the technical skills necessary to perform coronary angioplasty are transferable to the peripheral vasculature. However, an understanding of the natural history of peripheral disease, patient and lesion selection criteria, and the knowledge of other treatment alternatives are essential elements needed to perform these procedures safely and effectively. For interventional cardiologists who are inexperienced in the treatment of peripheral vascular disease, appropriate preparation and training, and a team approach (including an experienced vascular surgeon) are both desirable and necessary before attempting percutaneous peripheral angioplasty.

There are inherent advantages for patients when the interventionalist performing the procedure is also the clinician responsible for pre- and postprocedure care (analogous to the vascular surgeon who cares for patients before and after surgical procedures). Judgments regarding the indications, timing and risk-to-benefit ratio of procedures are enhanced by a long-term relation between physician and patient. Finally, in view of the increased incidence of coronary artery disease in patients with atherosclerotic peripheral vascular disease, the participation of a cardiologist seems appropriate.

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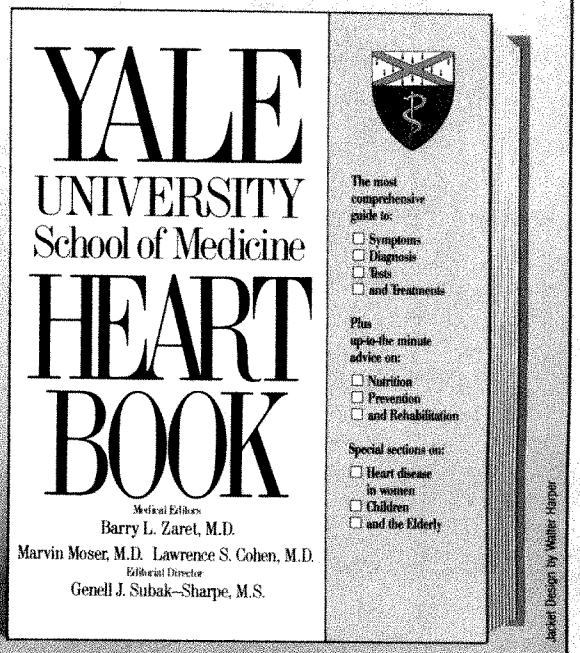
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Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and Lopressor slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, Lopressor should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered Lopressor, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Lopressor administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Lopressor therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, a $beta_2$-stimulating agent should be administered concomitantly, and the lowest possible dose of Lopressor should be used. In these circumstances it would be prudent initially to administer Lopressor in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Lopressor, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Lopressor should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction
Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with Lopressor, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, Lopressor should be discontinued.

Bradycardia: Lopressor produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, Lopressor should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

AV Block: Lopressor slows AV conduction and may produce significant first- (P-R interval ≥0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, Lopressor should be discontinued and atropine (0.25-0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, Lopressor should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, Lopressor may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent $beta_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should *not* be used prophylactically. If bronchospasm not related to congestive heart failure occurs, Lopressor should be discontinued. A theophylline derivative or a $beta_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and $beta_2$ agonists may produce serious cardiac arrhythmias.**

PRECAUTIONS

General
Lopressor should be used with caution in patients with impaired hepatic function.

Information for Patients
Patients should be advised to take Lopressor regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue Lopressor without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with Lopressor has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking Lopressor.

Laboratory Tests
Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions
Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Risk of Anaphylactic Reaction. While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to Lopressor was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C
Lopressor has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when Lopressor is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Lopressor is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when Lopressor is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Hypertension and Angina
Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS**.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see **WARNINGS**).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor.

Myocardial Infarction
Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of Lopressor and placebo described in the **CLINICAL PHARMACOLOGY** section, the following adverse reactions were reported:

	Lopressor	*Placebo*
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions
A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Lopressor.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **CONTRAINDICATIONS**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity
Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158-2460; rats, 3090-4670.

Signs and Symptoms
Potential signs and symptoms associated with overdosage with Lopressor are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment
There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see **WARNINGS, Myocardial Infarction**).

On the basis of the pharmacologic actions of Lopressor, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., levarterenol or dopamine.

Bronchospasm: A $beta_2$-stimulating agent and/or a theophylline derivative should be administered.

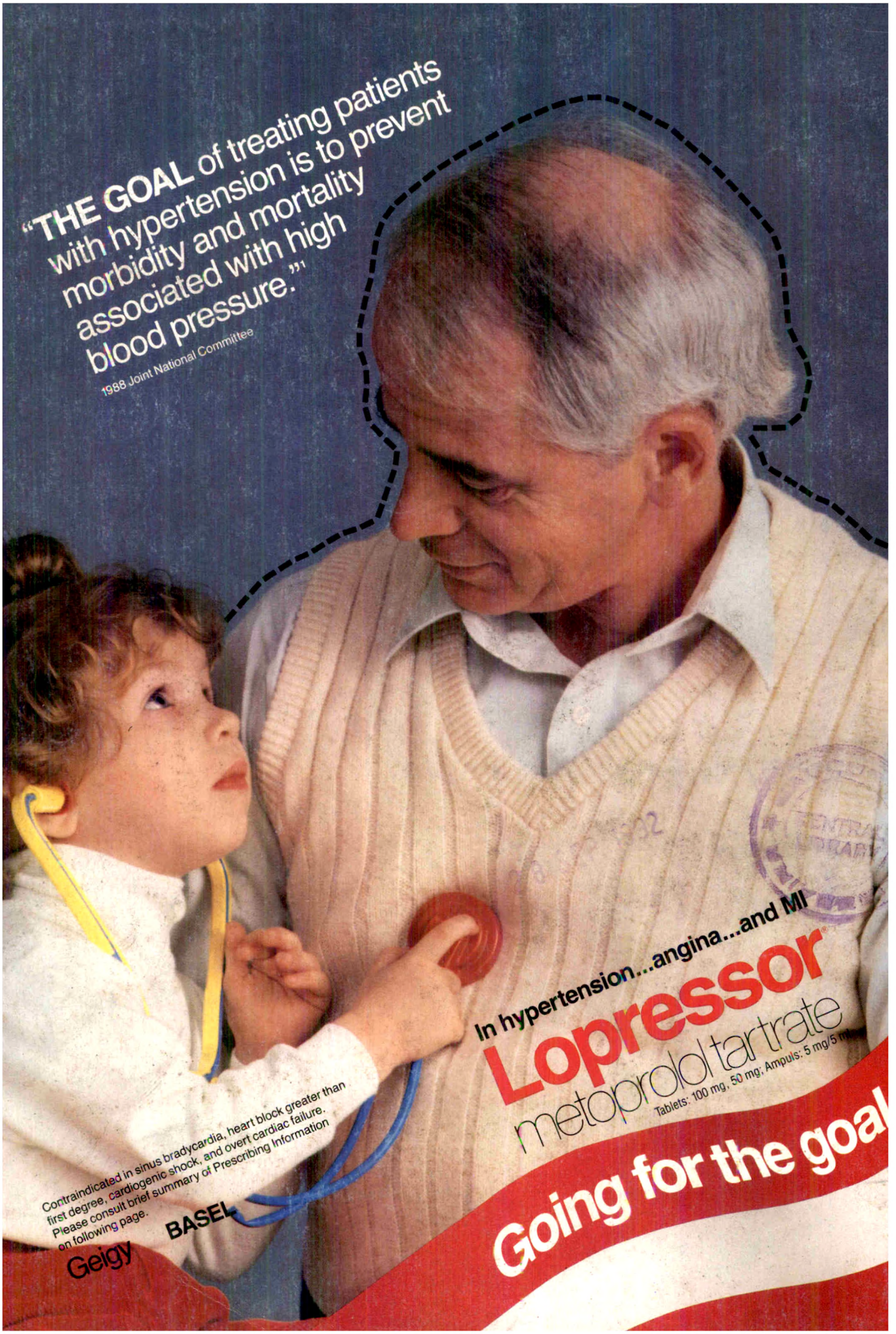
Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

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MAY 7, 1992

A Symposium: Beyond the Balloon: Complex Angioplasty for the Practitioner

GUEST EDITOR:

Robert A. Vogel, MD
Herbert Berger Professor of Medicine
Head, Division of Cardiology
University of Maryland
Baltimore, Maryland

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A SYMPOSIUM: BEYOND THE BALLOON: COMPLEX ANGIOPLASTY FOR THE PRACTITIONER

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The American Journal of Cardiology

Introduction

Robert A. Vogel, MD

Percutaneous transluminal coronary angioplasty (PTCA) has undergone a major evolution over the past decade. Improvements in operator technique and new equipment designs have improved primary success rates dramatically. The procedure is now common in certain high-risk patients with multiple vessel disease, multiple lesion dilation, advanced age, poor left ventricular function, or prior coronary bypass surgery. With improvements in mechanical design and diagnostic techniques and with the use of advanced imaging techniques during interventional procedures, practitioners now are able to go "beyond the balloon" in treating occlusions that previously were not amenable to balloon angioplasty alone.

Despite technical innovations, limitations of PTCA include restenosis and abrupt closure caused by coronary dissection spasm and thrombus formation at the site of dilation. These limitations have prompted investigators to explore alternative methods to maintain vessel patency. Our distinguished faculty describe some of these technologic advances and provide analyses of problem areas that must still be overcome.

James Margolis, of South Miami Hospital, presents data on recent experience with excimer laser coronary angioplasty (ELCA), showing the safety and efficacy of the technique in treating coronary stenosis, with results similar to those following PTCA. Among ELCA's key advantages for intravascular use is its ability to ablate atheroma without thermal injury. In comparison with conventional balloon angioplasty, ELCA may eliminate that component of restenosis due to elastic recoil of the luminal wall.

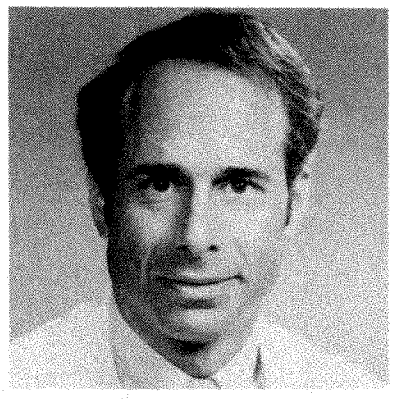
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With the vast experience, easy applicability, and excellent safety of PTCA, it is unlikely that any percutaneous revascularization modality will supersede this technology in general use, as noted by William O'Neill, of William Beaumont Hospital. However, new devices may be used to overcome the problems and deficiencies of angioplasty, and experience with atherectomy has shown that it holds most promise with lesions that are either elastic or too rigid to dilate, lesions that are complex and at high risk for dissection, restenosis lesions, and ostial lesions. Key advantages of atherectomy are a stable lumen after the procedure, a decrease in elastic recoil, and a smoother, less thrombogenic lumen. Further study using mechanical rotational atherectomy to partially debulk diffusely diseased vessels is also needed.

Paul Teirstein, of Scripps Clinic and Research Foundation, describes the technique of femorofemoral cardiopulmonary bypass, or "supported angioplasty," which has been shown to provide circulatory stability during high-risk PTCA. Cardiopulmonary support is a technically challenging procedure with significant patient morbidity. It has been shown, however, to help save lives of selected patients undergoing high-risk procedures.

In offering the "surgeon's perspective" on complex angioplasty, Robert Jones, of Duke University



Robert A. Vogel, MD

Medical Center, cautions that failed PTCA necessitating coronary artery bypass surgery accounts for a significant percentage of the complications of the procedure. Although most reasonable surgeons now have largely accepted the concept of nonoperative mechanical treatment of coronary artery disease, Jones notes that these same medical experts remain a valuable resource for constructive criticism regarding coronary anatomy without opening the chest.

In the article on the clinician's perspective on changing trends for surgical standby in patients undergoing PTCA, John Vogel, of the Santa Barbara Heart and Lung Institute and Goleta Valley Community Hospital, outlines his rationale for revising the 1988 guidelines of the American College of Cardiology and the American Heart Association, which recommend that an experienced cardiovascular surgical team be available within the institution for emergency surgery for all angioplasty procedures. With new technologies for angioplasty and an increased awareness of risk factors, active standby can be markedly reduced, thereby resulting in enormous cost reductions and in more appropriate patient care, according to Vogel.

We thank each of these distinguished participants for sharing their perspectives on the issues that practitioners must consider when selecting the most appropriate care for their patients.

Excimer Laser Coronary Angioplasty

James R. Margolis, MD, and Sameer Mehta, MD

Recent experience with excimer laser coronary angioplasty (ELCA) has shown the safety and efficacy of the technique in the treatment of coronary stenosis, with results similar to percutaneous transluminal coronary angioplasty (PTCA). Several advantages of the excimer laser for intravascular use have been identified by the ELCA Registry, a group of 15 institutions nationally that have pooled data on their cooperative experience with ELCA. Advantages include the ability of the laser to ablate atheroma with microscopic precision without thermal injury and the ability of vessel surfaces to heal without scarring. The initial results of the multicenter investigation of ELCA in 958 patients indicate that ELCA may be indicated particularly for long, diffuse lesions. With the advent of larger diameter catheters, ELCA is a viable alternative to PTCA. Restenosis was seen as a significant problem, and it remained problematic at 6-month follow-up. In comparison with conventional balloon angioplasty, ELCA may eliminate that component of restenosis due to inadequate dilation or elastic recoil, but it does not appear to affect restenosis caused by smooth muscle proliferation. Catheter design and energy delivery continue to evolve and may affect future results of laser coronary angioplasty.

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With the introduction of balloon angioplasty in the 1970s in the peripheral and coronary arteries, nonsurgical revascularization became a reality.[1] The procedure has seen unparalleled growth, with more than 500,000 balloon angioplasties projected to be performed annually in the United States by 1992.[2] Despite this increase, the technique has limitations. Problems with restenosis remain and for the most part are independent of technique; they occur most frequently in the superficial femoral and proximal left anterior descending arteries.[3] Success of the technique has been shown to vary inversely with the age and length of the occlusion, and dilation of diffusely narrowed arterial segments is not optimal.[3] Despite the therapeutic success of percutaneous transluminal coronary angioplasty (PTCA) in treating patients with obstructed vessels, the exact mechanism by which PTCA improves vessel patency remains unclear.[4]

When Andreas Gruentzig first reported a percutaneous approach to opening obstructed coronary arteries,[1] he was not implying that the technique he described would be the best way to perform PTCA.[5] The basic idea of displacing, rather than removing, atherosclerotic material presumes a better way to treat obstructive coronary heart disease. Severely disrupted intima inherent to the PTCA procedure results in either early closure or late restenosis.

To address these limitations, research has been directed to improving balloon catheter systems and developing a second generation of interventional devices that remove rather than displace atheroma. Both lines of research are aimed at developing devices that can simplify angioplasty techniques, extend them to previously unapproachable coronary artery lesions, and deal with the major problems of abrupt closure and late restenosis.

Such technologic advances in balloon catheter systems as improved steerable guidewire systems, low profile lubricated balloons, and monorail catheter systems have slowed impetus for development of second-generation devices. These advances have made it possible to reach quickly, easily, and safely virtually every extreme of the coronary arterial tree. Of all the second-generation devices either

available or under development, only the latest iterations of excimer laser catheters can equal the present generation of balloons for ease of use or ability to reach distal branches of a tortuous coronary anatomy.[5]

Despite progress with modern balloon catheter systems, however, certain anatomic situations remain difficult or impossible to treat with PTCA. These include diffuse disease, long lesions, calcified lesions, and chronic total occlusions. Improved catheter systems have not solved such problems as abrupt closure and late restenosis.[5] Although technologic advances in balloon catheter systems have slowed impetus for development of second-generation devices, these advances have now made possible delivery of the new devices into coronary arteries. Thus, these new developments have created an environment that has enabled excimer laser coronary angioplasty (ELCA) to emerge as a valuable clinical tool.

Theoretically, the appeal of laser angioplasty is its ability to debulk or remove the lesion, in contrast to balloon angioplasty, which compresses and tears the intima in the process of mechanically dilating the vessel.[6] Several laser systems have been studied for treating obstructive vascular disease.[3,7–10] The conventional continuous-wave lasers such as the neodymium: yttrium-aluminum-garnet (ND:YAG), argon ion, and carbon dioxide lasers destroy tissue by photothermal mechanisms. The energy from the absorbed photons is converted to heat that rapidly vaporizes the water within tissue.[3] To ablate vascular tissue photothermally, a requisite amount of tissue water must be present. Thus, ablation of densely calcified material with continuous-wave lasers is not possible.

The "hot tip" laser can potentially increase the number of patients suitable for angioplasty by safely recanalizing lesions that cannot be treated conventionally, but the long-term consequences of the technique are unknown.[11] In this technique, the laser catheter applies purely thermal energy to vascular tissue. It has been shown to be effective for angioplasty of relatively large peripheral arteries[11]; however, the coronary arteries are more vasoreactive and are less likely to tolerate thermal insult.

In treating the coronary arteries, using a laser system that ablates without creating heat is desirable. With pulsed laser systems, laser energy is delivered over only a small fraction of the lasing cycle, with heat dissipated between pulses. A pulsed laser system must be capable of delivering energies high enough to break chemical bonds directly within tissue; and for maximum efficiency, the laser wavelength should be one that is well absorbed by atheroma, collagen, and calcium.

The excimer system is the only clinically available pulsed laser system with the power to break chemical bonds directly. An advantage of this laser for intravascular use is that it ablates atheroma with microscopic precision without thermal injury. In experimental settings the vessel surface heals without scarring. The coronary laser angioplasty system developed by Advanced Interventional Systems (Irvine, California) couples a 308 nm excimer laser to multifiber over-the-wire catheters of 1.3, 1.6, 2.0, and 2.4 mm diameters with laser energy at 200–300 mJ/pulse. A unique feature is its long pulse width (>200 nsec), which permits delivery of high energies through smaller fibers than is possible with excimer systems that employ shorter pulse widths.[5]

The laser catheters are front firing, ablating only for a distance of 100 μm distal to their tips. Thus ablation occurs only when the catheter is in contact with tissue and the expected ablation rate is relatively slow. Because the laser ablates only on contact, lasering can be performed in a bloody field. Absorption of laser energy by blood offers a further margin of safety.[5]

To determine the feasibility of ELCA as an alternative or adjunct to conventional balloon angioplasty, 15 institutions are participating in a cooperative research effort: the ELCA Registry. Initial efforts have been aimed at testing the safety and the acute efficacy of early generation equipment, developing and perfecting clinical techniques, and improving catheter and laser design. The long-term goal is to evaluate the effect of ELCA on restenosis.

Current experience with excimer laser angioplasty is comparable to experience with balloon angioplasty in the early 1980s. Both the equipment and technique are evolving, and it will be several years before investigators gather sufficient data on long-term efficacy.

METHODS

In this study, 1,151 lesions in 958 patients from 15 centers were treated with laser angioplasty using a 308-nm XeCl excimer laser (Advanced Interventional Systems) coupled with multifiber over-the-wire catheters that were 1.3, 1.6, 2.0, and 2.4 mm in diameter (Table I).[12] The patient population consisted of 748 men (78%) and 210 women (22%) with a mean age of 61 years. Of the patients, 66% were in Canadian Cardiovascular Society classes

TABLE I ELCA Registry: Institutions and Principal Investigators

Cedars-Sinai Medical Center, Los Angeles: F. Litvack, N. Eigler
South Miami Hospital: J. Margolis, D. Krauthamer
St. Vincent's Hospital and Health Care Center, Indianapolis: D. Rothbaum, T. Linnemeier
Emory University Hospital, Atlanta: S. King, J. Douglas
Mayo Clinic, Rochester, MN: J. Bresnehan, G. Reeder
Georgetown University Hospital, Washington, DC: K. Kent, L. Satler
Methodist Hospital, Houston: W. Spencer, A. Raizner
Hoag Memorial Hospital Presbyterian, Newport Beach, VA: R. Haskell, P. McNalley
Philadelphia Heart Center: W. Untereker
St. Luke's Hospital, Phoenix: M. Vawter
St. Luke's Hospital, Milwaukee: F. Cummins, G. Dorros
Mercy Hospital of Pittsburgh: V. Krishnaswami
Goleta Valley Community Hospital, Santa Barbara: J. Vogel
Shands Hospital, Gainesville: G. Abela, J. Hill
Washington Hospital Medical Center, Washington, DC: M. Leon, G. Pichard

III or IV, 30% of the patients had undergone previous balloon angioplasty, and 26% had previous coronary artery bypass grafts. The demographic profile of the population was similar to that of a conventional balloon angioplasty cohort, with most patients severely symptomatic. Vessels treated were representative of the spectrum of disease treated with standard balloon angioplasty: 40% in the left anterior descending coronary artery, 18% in the left circumflex coronary artery, 33% in the right coronary artery, 8% in saphenous vein grafts, and 1% in the left main artery (Figure 1). Of the 1,151 lesions treated, 10% were total occlusions. More than half of the patients (52%) had lesions >10 mm and 22% had lesions >20 mm in length. The protocol included patients with stenoses or occlusions that could be crossed by a guidewire. Pretreatment of patients was identical to that for standard balloon angioplasty and included aspirin, heparin, and calcium antagonists. Conventional PTCA guiding catheters of 8, 9, or 10 F were employed.

TABLE II ELCA Registry: Definitions

Acute laser success
≥20% decrease of stenosis diameter and channel diameter (by laser alone)
>0.8 mm with 1.3 mm catheter
>1.0 mm with 1.6 mm catheter
>1.5 mm with 2.0 mm catheter
Procedure success
≥50% diameter lumen at end of procedure, with or without adjunctive balloon angioplasty

ELCA = excimer laser coronary angioplasty.

RESULTS

A procedure was considered successful with reduction in stenosis diameter of >20%, with the creation by laser alone of a channel diameter >0.8 mm with the 1.3 mm catheter, >1.0 mm with the 1.6 mm catheter, and >1.5 mm with the 2.0 mm catheter (Table II). Procedure success was defined as a final diameter lumen of ≥50% at the end of the procedure, whether or not adjunctive balloon angioplasty was performed.

According to these criteria, laser success was achieved in 967 of 1,136 lesions (85%) and procedure success was achieved in 1,059 lesions (93%) (Table III). On the basis of caliper measurements made by individual investigators, stenosis severity was reduced from 86% diameter stenosis at baseline to 48% post-ELCA and reduced to 25% following adjunctive balloon angioplasty, when it was required.

Quantitative coronary arteriography on a subset of 55 patients was essentially in agreement with the caliper measurements. Preangioplasty stenoses for this group were 83%, reduced to 49% after ELCA and 38% after PTCA. Using the more meaningful measurement of minimum luminal diameter, pre-ELCA stenoses were increased from a mean 0.5 mm to 1.6 mm post-ELCA to 2.1 mm post-PTCA. Since the 1.6 mm ELCA catheter was used in all of these stenoses, these data support the hypothesis

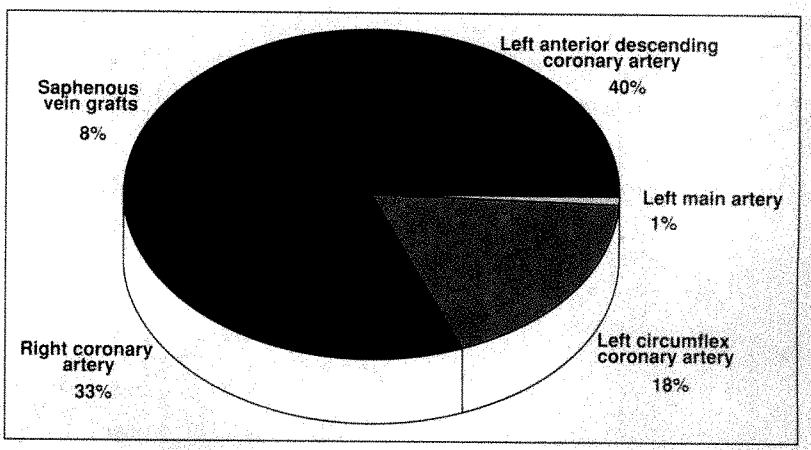


FIGURE 1. Percentages of vessels treated among 709 participants in ELCA registry; 30% of patients had previous PTCA. ELCA = excimer laser coronary angioplasty.

TABLE III ELCA Registry: Results (N = 1,136)		
Laser success (≥20% improvement)	967	(85%)
Procedure success (≤50% final obstruction*)	1,059	(93%)

*With or without adjunctive balloon angioplasty.

that the procedure works by ablation of atherosclerotic material rather than by stretching or "Dotter effect."

All lesion locations had comparable success rates, with success rates of 100% in the left main artery, 89% in the left anterior descending, 92% in the left circumflex, 93% in the right coronary artery, and 95% in saphenous vein grafts. Similarly, procedure success did not appear to be affected by lesion location. The success rate was 94% for stenoses and 91% for occlusions. This success rate is much higher than that normally associated with angioplasty of chronic total occlusions.

Figures 2–4 show various lesions pre- and post-ELCA. Figure 2 shows (A) a true lateral view projection of a diffusely diseased saphenous vein graft supplying the left anterior descending coronary artery, (B) with the insertion of a 2.0 mm laser catheter across the lesion, (C) the saphenous vein graft post-ELCA, and (D) the saphenous vein graft at 6-month follow-up. Figure 3 shows (A) a totally occluded left circumflex coronary artery, (B) the left circumflex immediately after ELCA, (C) after post-adjunctive PTCA, and (D) at 6-month follow-up. Figure 4 shows (A) a diffusely diseased and

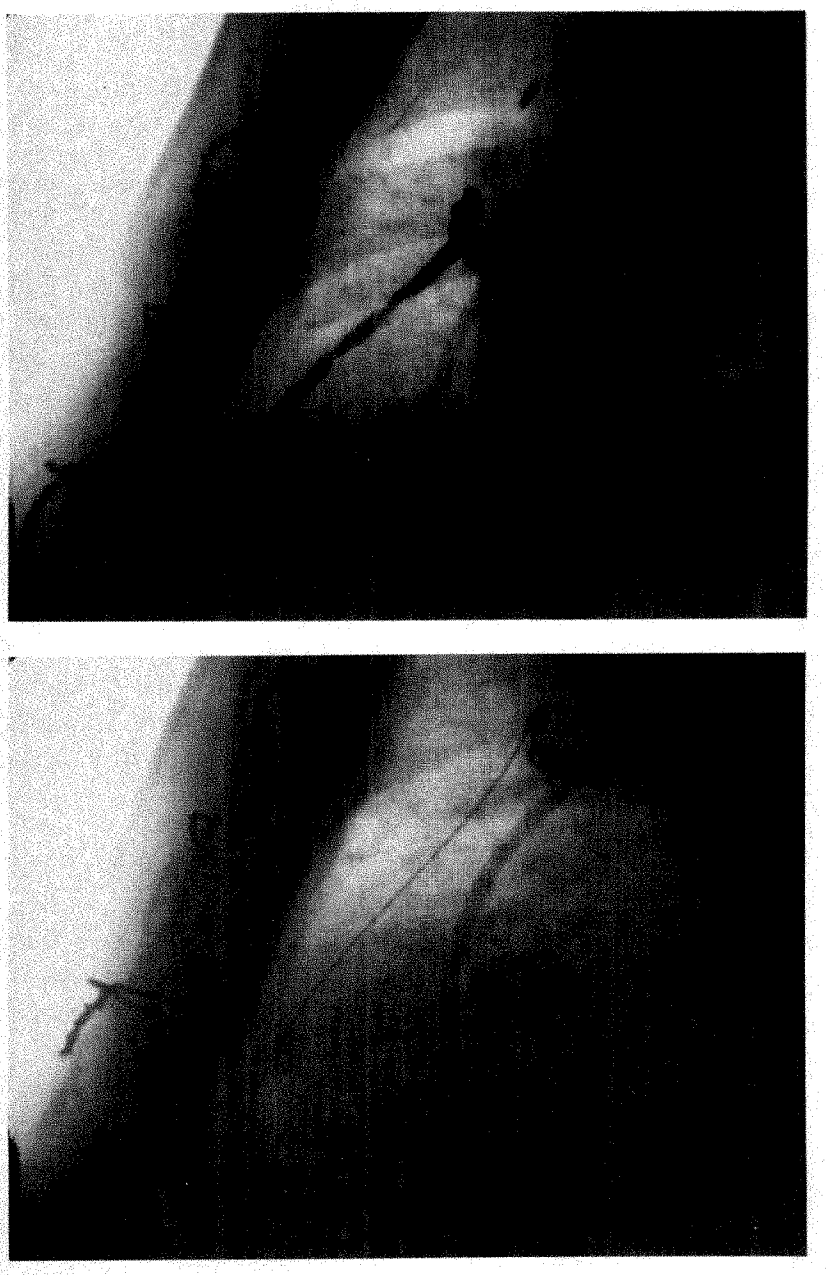


FIGURE 2. Diffusely diseased saphenous vein graft supplying the left anterior descending coronary artery, pre- and post-ELCA. True lateral view projection pre-ELCA (*A*); 2.0 mm laser catheter across lesion (*B*).

heavily calcified left anterior descending in true lateral projection, (B) with the insertion of a 2.0 mm laser catheter across the lesion, and (C) after stand-alone ELCA.

Lesion length did not affect acute success. Successful procedures were accomplished in 94% of lesions < 10 mm in length, 96% of lesions 10–19 mm in length, and 92% of lesions > 20 mm.

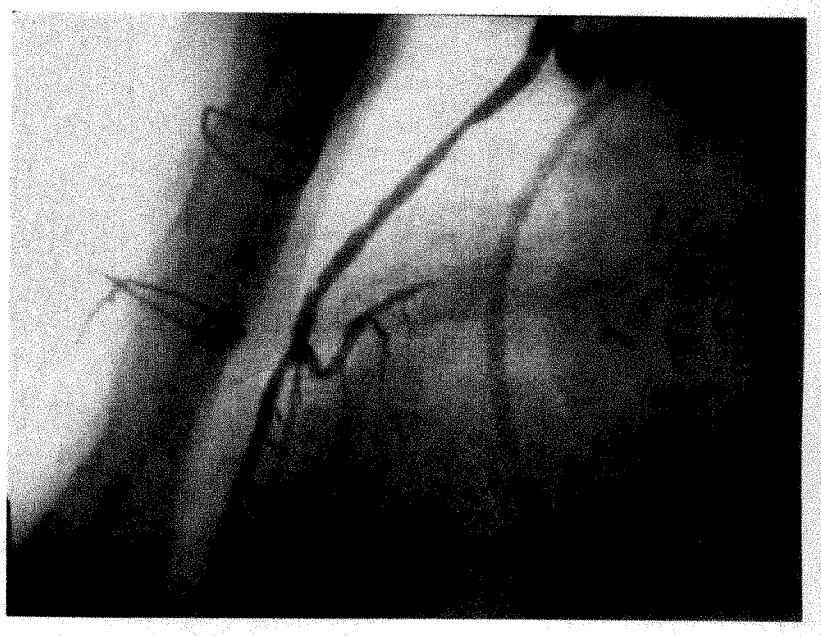
In nearly 75% of patients it was possible to achieve $\geq 50\%$ diameter lumen with laser alone. However, in a substantial number of these patients, adjunctive balloon angioplasty was performed in an attempt to achieve an optimal result.

The complication profile in the ELCA Registry is similar to that seen in a conventional balloon angioplasty population. Complications included 5.4% acute occlusion, 2% spasm, 1.9% thrombus, 1.1% perforation, 0.8% embolism, 0.5% aneurysm, 3.5% emergency coronary artery bypass graft surgery, 1.4% myocardial infarction, and 0.3% death. Perforation led to serious clinical sequelae requiring emergency surgery in only 50% of the perforation patients.

FOLLOW-UP EXPERIENCE

At 6-months, 88% of 812 patients were followed up and 58% had angiographic follow-up. As previously noted, procedure success was defined as $\leq 50\%$ diameter occlusion postprocedure, and angiographic restenosis was defined as loss of $> 50\%$ of the gain in lumen diameter and final stenosis of $> 50\%$ at follow-up. Clinical restenosis referred to





Post-ELCA (C) and at 6-month follow-up (*D*).

the occurrence of myocardial infarction, bypass surgery, death, reintervention, new and changing symptoms, or a positive treadmill test.

During the first 6 months, 1.4% of patients died, 1.5% had myocardial infarction, 7% had subsequent bypass surgery, 15% had repeat intervention (balloon angioplasty, laser angioplasty, or atherectomy), and 3.3% had new symptoms or a positive treadmill test. These results are similar to the PTCA experience reported by an American College of Cardiology/American Heart Association task force (Figure 5).[13]

The angiographic restenosis rate was 51% at 6-month follow-up, a rate believed to be related to the fact that fewer than 60% of patients had angiographic follow-up.

DISCUSSION

Although the angiographic restenosis rates appeared to be high (51%), this rate is attributed to the hypothesis that mostly symptomatic patients were restudied, whereas those who were feeling well refused to be reexamined. Thus, the data were skewed toward the symptomatic population. It is estimated that restenosis would be in the 40% range if all patients had been restudied.

The investigators did not identify any variables that were strongly related to restenosis. CCS class IV patients had a significantly higher angiographic restenosis rate than class 0 and class I patients (70% vs 38%). Lesion location also did not appear to be related to restenosis, and there was no indication that left anterior descending coronary

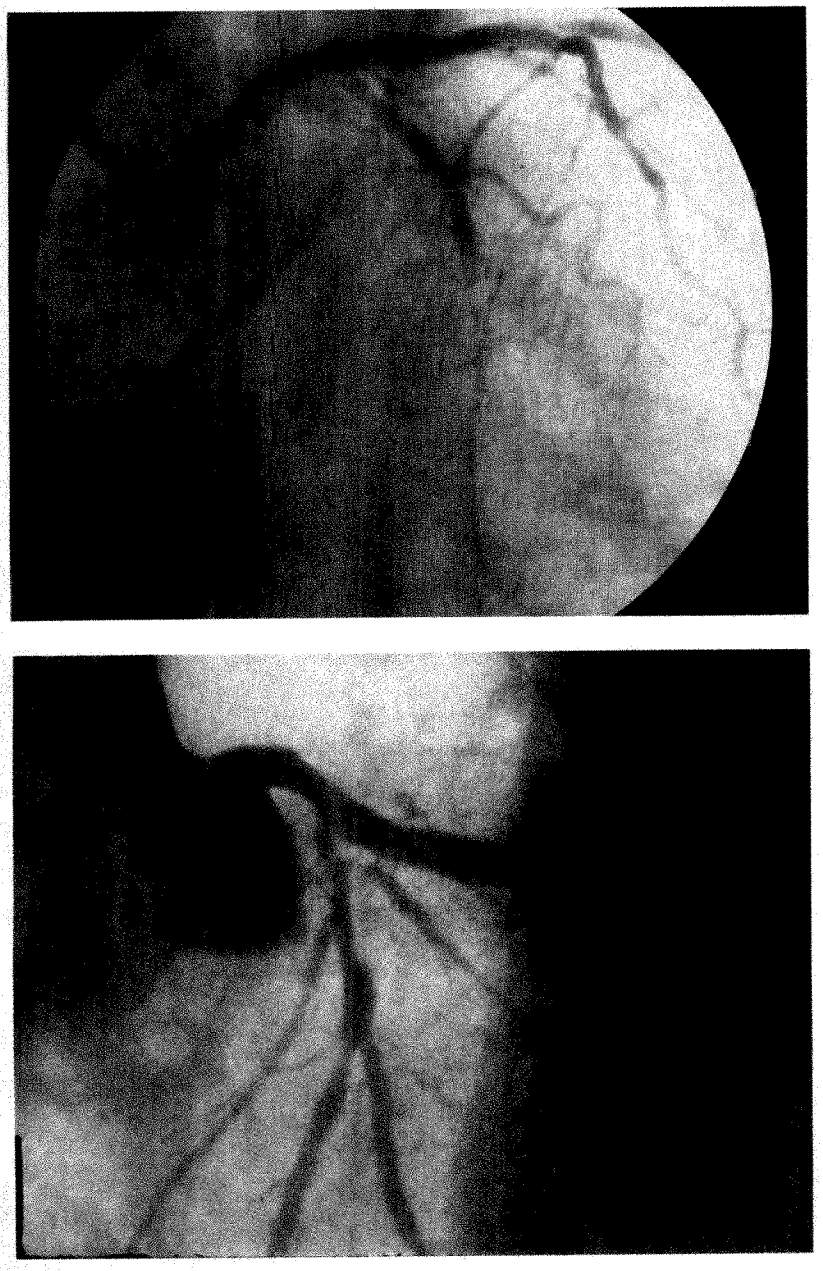


FIGURE 3. Totally occluded left circumflex coronary artery pre-ELCA (*A*); immediately after 1.6 ELCA (*B*).

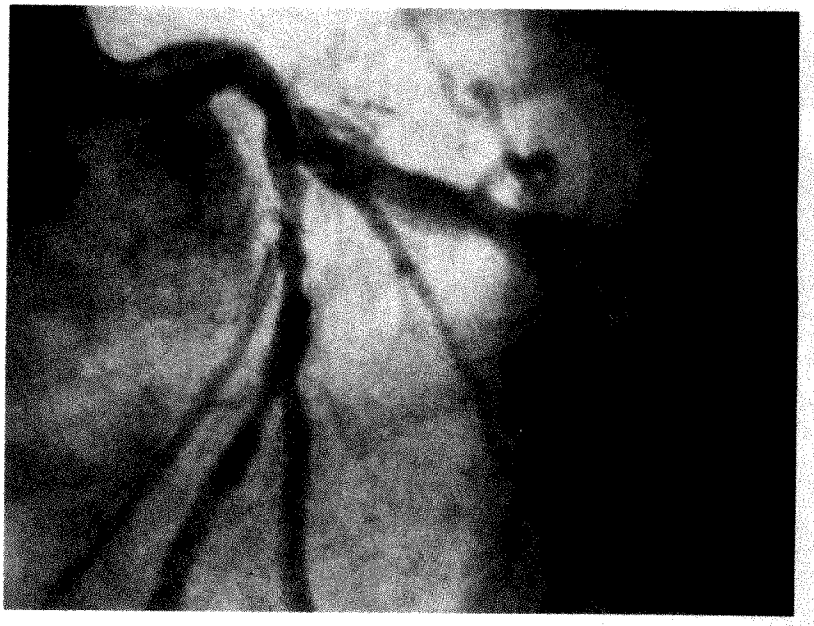
artery and vein graft lesions had more restenosis than did lesions in other locations. The data from the Miami group indicated that patients with lesions in the first centimeter of the left anterior descending coronary artery are excellent candidates for ELCA because insertion of a balloon in the left main artery is not needed. Most vein grafts were too large for ELCA, but ELCA was successful in the smaller vein grafts.

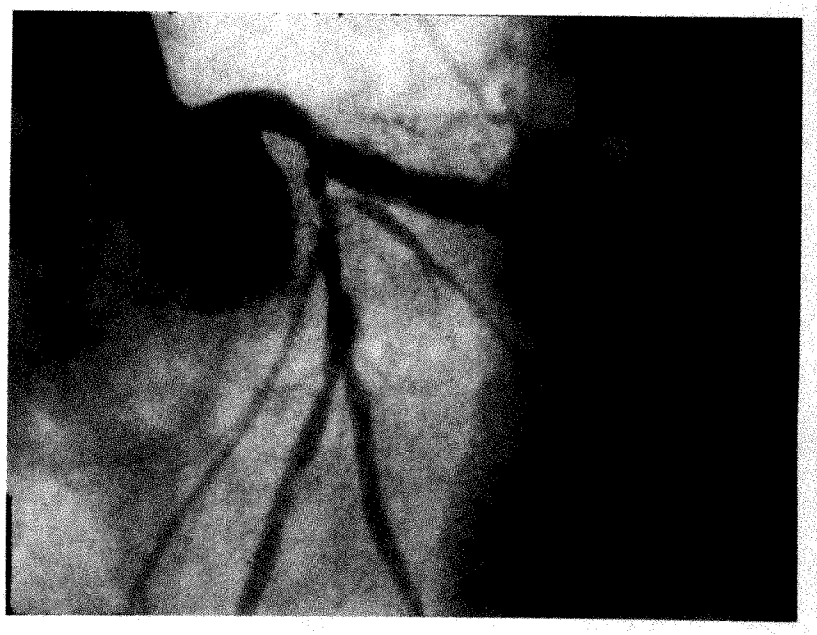
No significant difference in restenosis rates were seen in short lesions versus long lesions, de novo lesions versus redone lesions, stand-alone laser versus adjunctive angioplasty, 1.6 mm catheter versus 2.0 mm catheter, dissection versus no dissection, or in men versus women.

Two distinct populations were identified: a group of patients who had restenosis no matter what procedure was used, and a group of patients of comparable number who had restenosis only because their arteries were inadequately opened at the time of the original procedure. Changing the technique by using larger catheters and more liberal use of adjunctive balloon angioplasty should reduce the restenosis rate for this latter procedure.

MIAMI EXPERIENCE

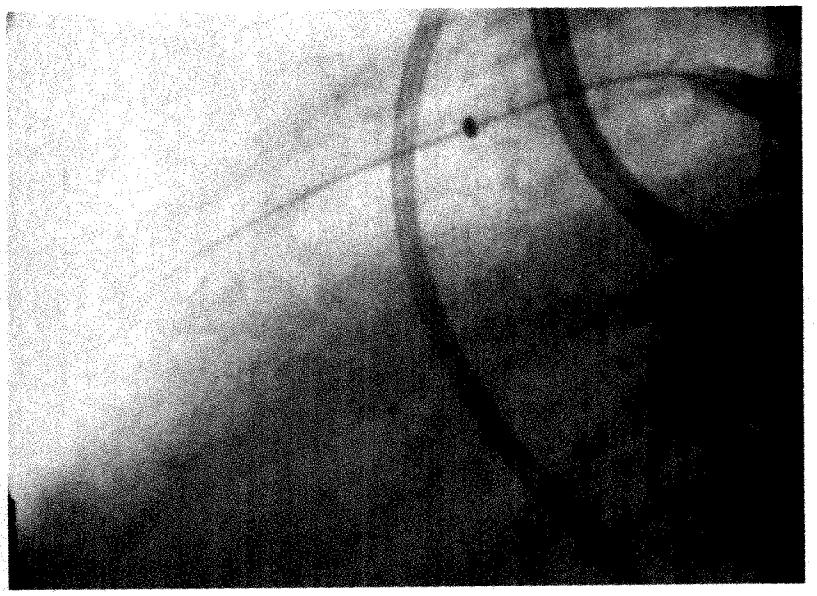
Data from Miami are of particular interest because they represent 25% of the entire ELCA registry. The demographic profile of the 227 Miami patients is similar to the entire registry series and not dissimilar to a conventional balloon angioplasty cohort. The majority of the Miami patients





Post-adjunctive PTCA (*C*); and at 6-month follow-up (*D*).





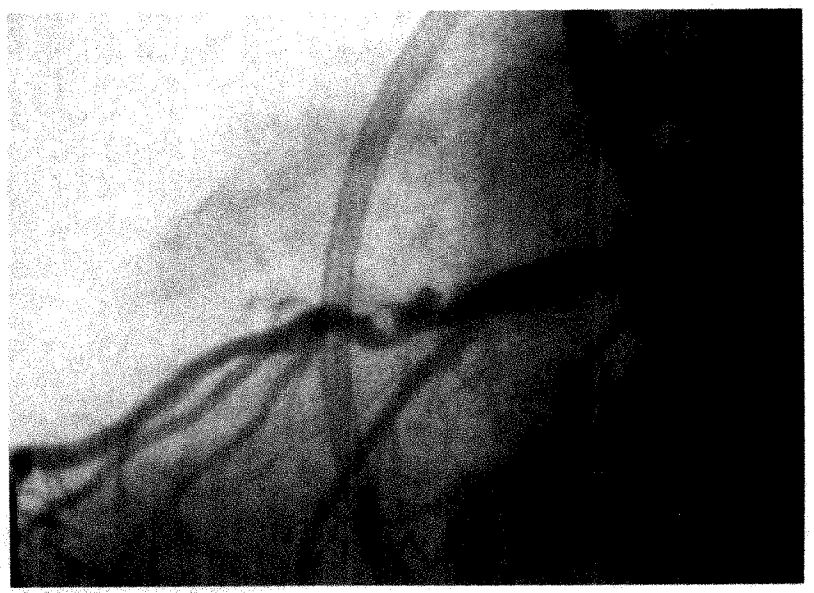


FIGURE 4. Diffusely diseased and heavily calcified left anterior descending coronary artery: true lateral projection (*A*); 2.0 mm laser catheter across lesion (*B*); and post-stand-alone ELCA (*C*).

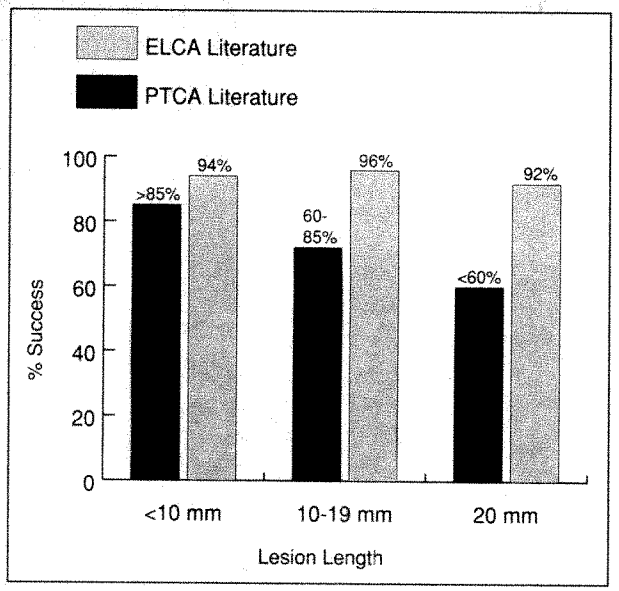


FIGURE 5. Success by lesion length: PTCA literature (See *Circulation*[13].) versus ELCA registry. ELCA: excimer laser coronary angioplasty; PTCA: percutaneous transluminal coronary angioplasty.

were severely symptomatic and had a larger proportion of left circumflex stenoses. Nearly 20% of lesions treated with ELCA in Miami were total occlusions, and 60% of all lesions were in the distal and middle segments of vessels (representing lesions not typically approached with other devices). Long lesions comprised 58% of the South Miami series.

Of the 309 lesions, laser success was achieved in 79% and procedure success in 97%. Of the 51 total occlusions, laser success was achieved in 78% and procedure success was achieved in all instances. This finding indicates that any time it was possible to get a guidewire across a total occlusion (no matter how old or how long the lesion), a successful result was obtained. Although a final diameter obstruction of <50% was achieved with the laser alone in 65% of lesions, adjunctive balloon angioplasty was used in approximately 50% of these. Only 37% of lesions were treated with laser alone. Introduction of the larger 2.0 mm catheter did not significantly improve the stand-alone laser rate.

Stenosis severity was reduced from 87% obstruction at baseline to 50% following ELCA to 27% following adjunctive balloon angioplasty when required. The complication profile of the Miami patients was somewhat better than that of the entire cohort. Two instances of perforation (0.6%) occurred. The emergency surgery rate was <1% and one death (0.4%) occurred.

CONCLUSION

These data on the excimer laser indicate that it is clearly applicable to all arterial segments and can be used in small and large arteries, vein grafts, long lesions, restenosis lesions, ostial lesions, chronic total occlusions, and calcified lesions. The device shows most promise in long lesions and for treating ostial stenoses, chronic total occlusions, and calcified lesions.

ELCA can be performed safely, with no more risk than that for conventional PTCA. It is a viable alternative to balloon angioplasty and will be used more frequently with the advent of larger diameter catheters. Excimer laser coronary angioplasty may be ideal for long diffuse or calcified stenoses and for chronic total occlusions. In comparison with conventional balloon angioplasty, ELCA may eliminate the component of restenosis due to inadequate dilation or elastic recoil.

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Mechanical Rotational Atherectomy

William W. O'Neill, MD

Percutaneous transluminal coronary angioplasty (PTCA) is practiced widely in the United States and is indicated for the majority of stenosed vessels that have de novo, type A lesions. Despite extensive experience with the procedure and improvements in balloon technology, periprocedural dissection and restenosis remain major limitations of PTCA. Research indicates that certain lesion types and patient populations may be treated more effectively with other technologies. New mechanical devices have been designed to help improve the safety of PTCA and hold promise for correcting coronary dissection and abrupt closure—the sources of such angioplasty complications as myocardial infarction, urgent bypass surgery, and death. Among the results achieved with the new atherectomy techniques are a more stable lumen after atherectomy; a decrease in elastic recoil; a smoother, less thrombogenic lumen; and the feasibility of extensive debulking or endarterectomy. Experience indicates that mechanical rotational atherectomy will be an extremely useful addition to the armamentarium for percutaneous revascularization.

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With the vast experience, easy applicability, and excellent safety record of balloon angioplasty, it is unlikely that any percutaneous revascularization modality will supersede this technology in general use. However, new devices must be used to overcome the problems and deficiencies of angioplasty. These problems include a persistent rate of coronary dissection, coronary restenosis, poor efficacy in total coronary occlusions, poor results in elastic lesions, and lesions too stenotic to penetrate successfully.

Atherectomy clearly can assist in overcoming some of those problem areas. Research indicates that the subgroups in which atherectomy shows promise include lesions that are elastic or too rigid to dilate, lesions that are complex and at high risk for dissection, restenosis lesions, and ostial lesions. Further study using mechanical rotational atherectomy to partially debulk diffusely diseased vessels also is needed. Among the advantages of atherectomy are a stable lumen after the procedure, a decrease in elastic recoil, and a smoother, less thrombogenic lumen. Our experience indicates that mechanical rotational atherectomy will be extremely useful in percutaneous revascularization.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Percutaneous transluminal coronary angioplasty (PTCA) has achieved widespread clinical acceptance in the United States. The technique allows effective treatment of patients with coronary artery disease without the surgical procedure entailed by coronary artery bypass grafts. It has surpassed coronary artery bypass surgery in procedural volume in the United States. Despite its widespread use, PTCA has major limitations and is not optimal therapy for some types of lesions. Several other types of catheter-delivered implements have been designed to address these limitations.

PTCA is still indicated for diseased vessels that have de novo, type A lesions. However, certain lesion types and patient populations may be treated more effectively with other technologies.

Procedural safety of PTCA: Periprocedural abrupt closure is the most serious complication of PTCA. Despite extensive experience with the procedure and improvements in balloon technology, the incidence of this complication has remained steady at 2–5%.[1]

The recently published National Heart, Lung, and Blood Institute registry documented a 6.8% incidence of periprocedural abrupt occlusion among 1,801 patients, and 4.7% incidence among 2,891 lesions.[1] The incidence of occlusion in the catheterization laboratory was 4.9%; the incidence of postprocedure occlusion was 1.9%. Several demographic factors were associated with increased risk for periprocedural occlusion; it occurred at a 9.9% rate in 312 patients with acute coronary insufficiency, compared with a 6.0% rate in patients without this condition ($p < 0.05$). Other factors significantly associated with periprocedural occlusion were 3-vessel disease (9.8% incidence in 367 patients, compared with 6.1% for 2-vessel and 6.0% for 1-vessel disease), and inoperable or high-risk surgical status (12.3% incidence in 138 patients compared with 6.3% in other patients).

Lesion factors significantly associated with periprocedural occlusion included stenosis of $\geq 90\%$ vessel diameter, diffuse or multiple discrete disease, lesions in segments supplying collaterals, and evidence of thrombus or calcification. Intimal tears occurred in 780 of 2,882 lesions (27%) and extensive dissection occurred in 89 of 2,891 lesions (3%).[1] These procedural events were most significantly associated with occlusion. Occlusion occurred in 9.9% of patients with intimal tears compared with 2.7% of others ($p < 0.001$), and in 21.3% of patients with dissection compared with 4.2% of others.

Periprocedural occlusion increases morbidity and mortality in PTCA patients. In-hospital mortality was approximately 5% in patients with this complication, compared with 1% in other patients. In-hospital infarctions in patients with occlusions ranged from 27% in patients with transient occlusions to 56% in patients treated surgically, compared with 2% in nonoccluded patients. Long-term (2-year) infarction rates were roughly the same for patients with and without periprocedural occlusions, and 2-year rates of PTCA also were comparable (approximately 23%). However, periprocedural occlusion remained associated with increased mortality.[1]

Bansal et al[2] have studied risk factors for arterial dissection in PTCA to identify patients who may be at high risk for dissection and, thus, for periprocedural occlusion. In this study, we examined the balloon inflation rate to test the hypothesis that rapid balloon inflation increases the risk of dissection. In this randomized trial, no significant difference in dissection rates was found between gradual balloon inflation over 30 seconds and rapid balloon inflation in <5 seconds in 142 lesions. However, the association of dissection with complex lesion morphology was highly significant ($p = 0.00001$); dissection occurred in 33% (8/24) of type A lesions, 63% (57/91) of type B lesions, and 96% (26/27) of type C lesions.

Periprocedural occlusion, or even the temporary occlusion resulting from balloon inflation, can result in hemodynamic collapse. This event can be especially dangerous to individuals who have poor ventricular function or a single remaining patent coronary conduit. A multicenter study indicates that the morbidity and mortality associated with PTCA in such high-risk patients can be reduced with the addition of cardiopulmonary bypass to the procedure.[3] In 105 patients with an ejection fraction $<25\%$ or a target vessel supplying $>50\%$ at the myocardium, the overall hospital mortality rate was 7.6%. This rate was only 2.6% in patients who were younger than age 75 and not affected by left main coronary artery stenosis. The mortality rate was 60% for patients with abrupt occlusion after discharge from the catheterization laboratory. Thus, dissection and abrupt occlusion are most dangerous in high-risk patients. In these patients, it is imperative that an optimal angiographic result be achieved.

PTCA has a number of benefits. Overall, it has extremely low rates of mortality and need for emergency bypass surgery. Elective cases also are associated with extremely high success rates. PTCA also is a simple procedure. An ongoing study of the procedure at William Beaumont Hospital[4] indicates that conventional postprocedure heparin therapy may be eliminated with no detrimental effect on patient outcomes. In 200 patients (of a planned 400), 22% of patients in the no-heparin group have been able to go home on the day of the procedure, and a total of 42% have gone home within 24 hours.

Thus, PTCA remains an important and appropriate procedure for the majority of lesions. Yet, it falls short of optimal therapy in many cases involving complex morphology or high-risk patients.

Limiting factors in PTCA: Coronary restenosis is a second major limitation of PTCA. Many factors contribute to the incidence of restenosis and some of these factors are inherent in PTCA. Up to 30%

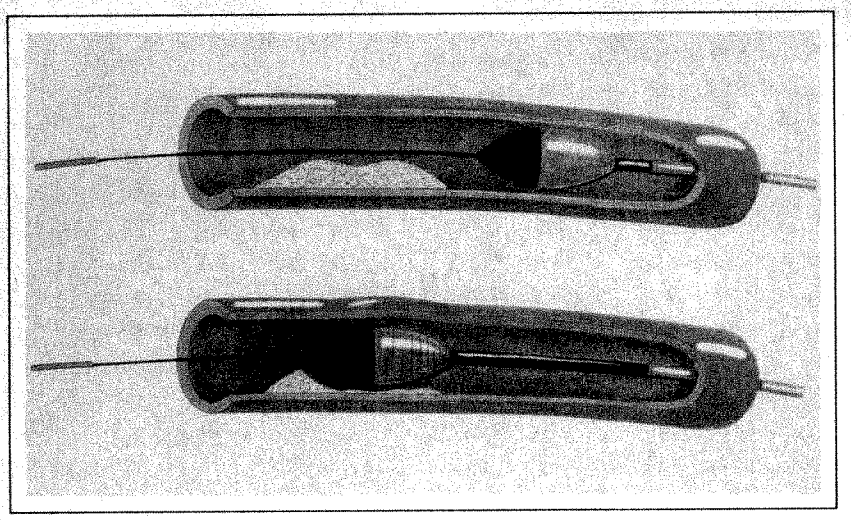


FIGURE 1. The Auth high-speed rotary atherectomy device. A brass burr coated with diamond chips is welded to a drive shaft that is rotated at high speed. The device is inserted over a guide wire, and placement is directed by fluoroscopy.

of restenotic vessels exhibit elastic recoil, limiting the ability of the balloon to relieve the obstruction.[5] The inflated balloon can also cause deep medial smooth muscle injury. This stimulates smooth muscle proliferation in the vessel, contributing to restenosis. Finally, PTCA leaves ragged, irregular lesions in the lumen, which stimulate platelet and fibrin deposition.

Several other technical problems limit the efficacy of PTCA in certain cases. Current balloon and guide wire technology is unable to recanalize total coronary occlusions or fibrotic, elastic lesions such as those in ostial locations. Other lesions that are too severe, hard, or calcified may not allow passage of the balloon even after guide wire placement, and some rare lesions simply do not respond to balloon inflations.

MECHANICAL ATHERECTOMY

The clinical need for improved technology was recognized in the early 1980s. Although some investigators initially supported coronary laser angioplasty in the late 1970s,[6] high rates of perforation and thrombosis dampened enthusiasm for this treatment modality. Others began to investigate the feasibility of mechanical peripheral and coronary atherectomy.[7–9] Among the results achieved with the new atherectomy techniques are a more stable lumen after atherectomy; a decrease in elastic recoil; a smoother, less thrombogenic lumen; and the feasibility of extensive debulking or endarterectomy.

Mechanical rotational atherectomy: Auth et al have developed a high-speed rotary atherectomy device inserted over a guide wire and directed with fluoroscopy.[8] The device consists of a brass burr coated with diamond chips measuring 30–120 μm in diameter (Figure 1). Available in various sizes, the burr is selected to match the diameter of the vessel being treated. The burr is welded to a drive shaft that is rotated by a turbine at high speeds.

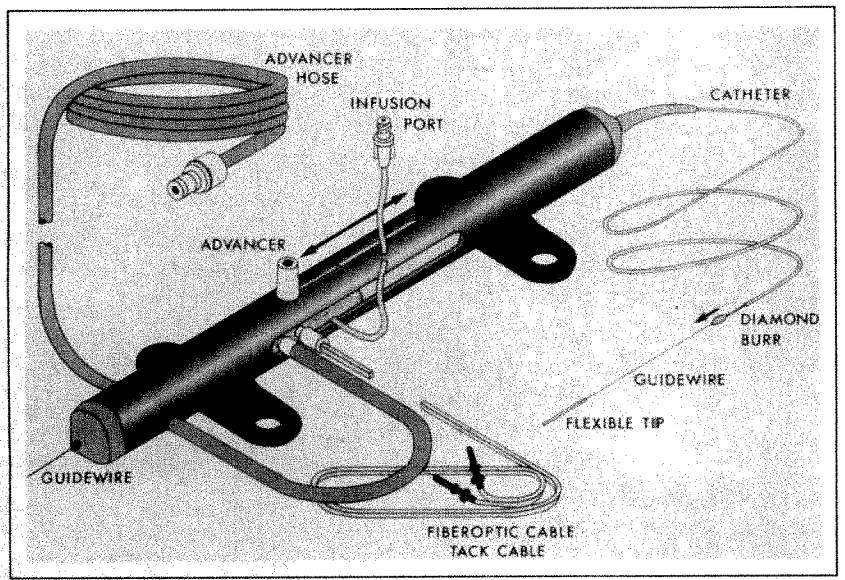


FIGURE 2. The Rotablator (Heart Technology, Inc., Bellevue, Washington) operates at 160,000–190,000 rpm.

Commercial models (e.g., Rotablator, Heart Technology, Bellevue, Washington) rotate at speeds of 160,000–190,000 rpm (Figure 2). The rotating burr selectively removes hard tissue, whereas soft tissue is deflected by the elastic recoil of normal segments of vessel. The device thus selectively ablates the firmer atherosclerotic plaque. The tissue is chipped off as microparticles and embolizes downstream.

Microparticle embolization was an early concern with this device. When the device was tested on 68 cadaver arteries, however, the pulverized atheroma particles (in colloidal suspension) were generally smaller than red blood cells, and injection of the suspension into canine femoral arteries failed to produce tissue injury.[8] We further analyzed the impact of atheromatous microparticles on canine coronary blood flow and found no deleterious effects.[10] In our experience with rotary atherectomy we have seen no significant adverse effects of microparticle embolization.

A series of 39 patients treated at William Beaumont Hospital showed no impairment of regional function or ventricular wall motion with this device (Figure 3). In procedures involving the right coronary arteries or circumflex artery, bradycardia, transient complete heart block, or transient asystole is invariably seen.

A recent multicenter study[11] of percutaneous transluminal coronary rotational ablation in 315 patients reported no in-hospital deaths and a 95% rate of acute success (<50% residual stenosis). Of all lesions, 87% were complex (type B or C). Complications included myocardial infarction in 5.6% of patients and urgent coronary artery bypass graft in 1.6%. There were 26 cases (8.2%) of angiographic evidence of flap or dissection. Only one case required a coronary artery bypass graft.[12] Percutaneous transluminal coronary rotational ablation also has shown excellent results in lesions that have unfavorable morphologic characteristics, including eccentricity, calcification, tortuosity, and location at a bifurcation.[13] In our experience, type C lesions appear to be better treated with rotational ablation (Table I).

TABLE I Results of Mechanical Rotational Ablation of Type C Lesions

Outcome	MRA (n = 27)	PTCA (n = 196)	p Value
Successful	26 (96%)	149 (76%)	<0.03
Major cardiac event	1 (3.7%)	11 (5.6%)	NS
Emergency CABG	1 (3.7%)	5 (2.6%)	NS
Abrupt closure	0	4 (2.0%)	NS
Death	0	2 (1.0%)	NS

CABG = coronary bypass surgery; MRA = mechanical rotational ablation; NS = not significant; PTCA = percutaneous transluminal coronary angioplasty.

Follow-up at 6 months in 94% of patients in the multicenter study showed a restenosis rate of 32%.[11] The following have been identified as risk factors for coronary restenosis following rotation angioplasty: lesions in the left anterior descending coronary artery, ostial and proximal lesions, and lesions in saphenous vein bypass grafts.[14]

The Rotablator may be useful in cases of restenosis after PTCA. Ostial lesions also are appropriate for mechanical rotational atherectomy treatment, as are heavily calcified lesions, diffusely diseased arteries, and lesions at bend points in the vessel. Heavily calcified lesions and lesions at bend points should not be treated with a transluminal extraction catheter or directional coronary atherectomy.

Unlike balloon angioplasty, the high-speed rotary burr grinds atheroma into fine particles that pass harmlessly through the capillary circulation. Furthermore, rotary atherectomy leaves a smooth, polished intraluminal surface and no intimal flaps. Unlike the laser, its energy requirements are minimal, its machinery is trim, and it selectively removes rigid tissue such as calcified or fibrous

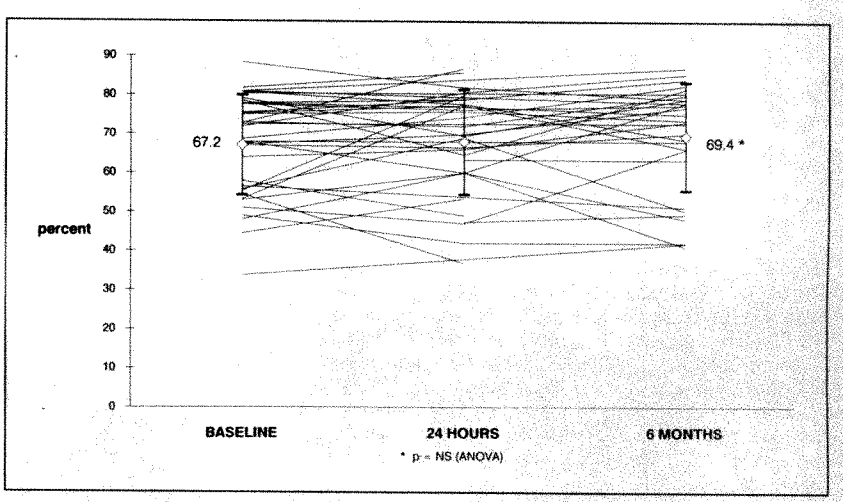


FIGURE 3. Ejection fraction changes with mechanical rotational atherectomy employing the Rotablator catheter. The global ejection fraction was serially assessed in 39 patients treated. No deterioration in ventricular function was noted between studies obtained at baseline, at 24 hours, and at 6 months post-catheterization. NS = difference not significant (ANOVA).

atherosclerotic plaque, whereas rubbery or elastic tissue, such as the outer media, remains relatively uninjured.[8]

Despite these advantages, the Auth device needs further improvement. Investigators have identified problems with the guide wire that lead to perforation or inability to pass the guide wire past totally occluded arteries.[8] The atherectomy burr is relatively ineffective for arteries completely occluded with chronic thrombus. Finally, large vessels cannot be completely treated by this device alone.

Directional coronary atherectomy: Simpson and colleagues at Sequoia Hospital in Redwood City, California, have developed a technique called directional coronary atherectomy.[15] The Atherocath is characterized by a cylindrical metal housing attached to the end of a braided double-lumen catheter. The cylindrical housing has a "longitudinal window" that can be positioned snugly against the atheroma with the help of a small balloon opposite the window. Inside the window, a rotating cutter blade shaves off atherosclerotic material and deposits it in the distal part of the metal housing. A separate hand-held battery-powered motor drive is attached to a cable connected to the cutter blade.

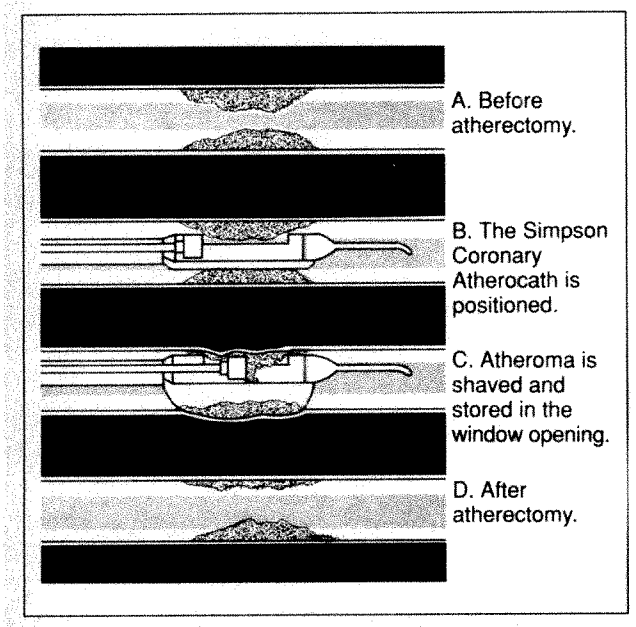


FIGURE 4. The Simpson Coronary Atherocath (John B. Simpson, MD, Sequoia Hospital, Redwood City, California) is a directional device. A cylindrical metal housing with a 10 mm window runs along one side and a balloon along the opposite side. A cylindrical cutter within the housing is powered by a hand-held motor. Under fluoroscopy, the distal end of the catheter is placed across the stenosis and the balloon is inflated to 30 psi to hold the housing against the stenosis. The motor is turned on and the cutter is advanced, shaving off any atheroma that protrudes into the window opening. The shavings are pushed forward and stored in a collection chamber, and the device is repositioned for any necessary additional passes. *A*, before atherectomy; *B*, the Atherocath is positioned; *C*, atheroma is shaved and stored in the window opening; *D*, after atherectomy.

During a procedure, the Atherocath is advanced over the wire under fluoroscopic guidance (Figure 4). The window of the cylindrical housing is positioned across the stenosis. The positioning balloon is inflated, the attached motor drive is activated, and the cutter blade is slowly advanced through the metal housing, shaving off atheroma and depositing it distally. The positioning balloon is deflated, the catheter is torqued about 60–90° to reposition the window and to remove additional atheroma. When the collection chamber is full, the catheter is withdrawn from the patient and the cutter blade retracted into the proximal portion of the housing. Repeated passes are made until the desired result is achieved.[16] Simpson and colleagues recently reported their experience in 502 procedures (578 lesions).[15] Patients' mean age was 59 years and 42% had unstable angina. Sixteen of the procedures were performed as salvage for failed PTCA, and 55% of the lesions treated had been previously treated with angioplasty. The overall success rate was 88.2%, with individual vessel success rates ranging from 79% in the left anterior descending coronary artery (n = 279) to 100% in the diagonal artery (n = 3).

A multicenter study of this technique[17] reported a 4.2% rate of abrupt closure (periprocedural stenosis) in 1,018 procedures (1,138 lesions), a rate roughly comparable to the rates seen with PTCA and mechanical rotational atherectomy. Among the risk factors identified were right coronary artery lesions, de novo lesions, and eccentric lesions. Abrupt closure was less frequent during procedures on saphenous vein grafts.

The Sequoia group investigated the effect of angiographic risk factors on the outcome of directional coronary atherectomy in a series of 499 lesions in 441 procedures.[18] The overall success rate was 88% per lesion (87% per procedure). The investigators evaluated several risk factors for their effect on patient outcome, including lesion eccentricity, abnormal contour, ostial location, and length >10 mm. Only calcification and diffuse disease were significantly associated with failed procedures. In 211 successfully treated lesions followed up angiographically at 3–12 months (or earlier if symptoms recurred), the overall restenosis rate was 36%: 29% (24/82) for de novo lesions and 40% (52/129) for restenosis lesions.[19] Factors significantly associated with restenosis were lesion length >10 mm, vessel diameter <3 mm, and overdilation.[19] This group has also used directional coro-

nary atherectomy successfully in rescue procedures for failed PTCA (success in 87% of 30 patients)[20] and in saphenous vein graft lesions (91% success rate in 87 lesions).[21] However, restenosis rates are high in vein graft lesions, especially those treated previously with PTCA.

Appropriate indications for directional coronary atherectomy include ostial lesions and focal lesions. De novo lesions can be treated effectively and have a very low risk of restenosis. Highly eccentric lesions in the left anterior descending artery are well suited to directional coronary atherectomy. Directional coronary atherectomy is also effective as a bailout device for discrete occlusive flaps present after PTCA. Heavily calcified lesions and lesions at bend points should not be treated with directional coronary atherectomy.

Transluminal extraction catheter: Another type of intraluminal catheter atherectomy device is the transluminal extraction catheter, which allows the transluminal extraction of atherosclerotic plaque, thus reducing the risks of downstream embolization and leaving a smooth, undissected lumen.[7] It consists of a rotary cutting device advanced over a 0.014 inch PTCA guide wire (Figure 5). The flexible torque tube device is introduced percutaneously and tracks over the flexible steerable guide wire under fluoroscopic control. When the radiopaque tip is properly positioned near the origin of the lesion, a 2-stage trigger is activated on the hand-held control piece. The conical cutter rotates at 750 rpm while suction is applied through the opening of the cutting window to extract the plaque fragments through the catheter and out of the patient's body.[15] The device is well suited for large, bulky lesions with extensive intraluminal thrombus.

Stack et al[9] demonstrated the safety and efficacy of the device in reducing stenosis and increasing flow in peripheral vascular disease. They treated 71 atherosclerotic lesions during 41 procedures in 41 extremities of 36 patients. The procedural success rate was 98% (40/41), with success defined as $\leq 50\%$ residual stenosis in all lesions; the patient success rate was 97% (35/36). Mean luminal diameter stenosis was reduced from $72 \pm 17\%$ to $29 \pm 16\%$ ($p < 0.0001$). No arteriographic or clinical signs of distal embolization were present and no vessel perforations occurred.

The transluminal extraction catheter has also shown good results in treatment of coronary lesions, even those normally deemed unfavorable for PTCA. Leon et al[22] recently reviewed the transluminal extraction catheter for efficacy, safety, and long-term reocclusion in 281 patients with recent acute myocardial infarction, diffuse disease, ostial disease, or eccentric lesions. In 31 patients with recent myocardial infarction, efficacy was 97%, although 66% of patients required both the transluminal extraction catheter and PTCA. Efficacy was defined as $\geq 20\%$ reduction with the transluminal extraction catheter alone or $\leq 50\%$ residual stenosis with the transluminal extraction catheter and PTCA. Efficacy was high ($> 90\%$) for all lesion subsets, and few complications were reported. Eccentric lesions were associated with a slightly lower success rate than concentric lesions (91% vs 95%), and with a slightly higher complication rate (7% vs 2%). Restenosis rates assessed angiographically at 6-month follow-up were similar to those reported for PTCA.

The transluminal extraction catheter has shown beneficial results in saphenous vein grafts.[23–24] Ostial lesions may be treated with the transluminal extraction catheter device, as well as with high-speed rotary atherectomy or directional coronary atherectomy. The transluminal extraction catheter device is appropriate for ulcerated saphenous vein grafts or those that have a very large clot burden. It is also effective for native coronaries with extensive intraluminal thrombus. Heavily calcified lesions and lesions at bend points should not be treated with the transluminal extraction catheter or directional coronary atherectomy. Ultimately, the greatest utility for this device will be in vessels containing thrombus, including patients with evolving myocardial infarction.

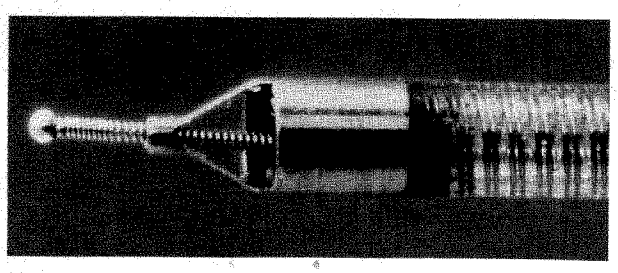


FIGURE 5. Stack Transluminal Extraction Catheter (Interventional Technologies, San Diego, California). Like the Auth device, this device also travels along a guide wire and uses a vacuum to extract microparticles and prevent particulate embolization. Potential advantages include the lack of distal particulate embolization and the ability of the device to extract atheromatous material without changing the catheter housing during the procedure.

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Cardiopulmonary Support

Paul S. Teirstein, MD

Cardiopulmonary support (CPS) has been shown to be a useful addition to interventional cardiology when considering alternatives for high-risk patients. Cardiopulmonary support systems are capable of up to 6 liters/min output and can be used prophylactically to prevent hemodynamic collapse following balloon occlusions or acute vessel closure. The technique, supported angioplasty, results in reductions of preload and afterload and allows prolonged balloon inflations in critical coronary vessels. Although it provides excellent support for most high-risk patients, CPS is a technically challenging and expensive procedure associated with significant patient morbidity. Standby CPS patients are prepared for institution of CPS, but bypass is not actually initiated unless the patient sustains irreversible hemodynamic compromise. In this study, standby and prophylactic patients had comparable success and major complication rates, but procedural morbidity was more frequent in prophylactic patients. Further study will better define appropriate patient selection for standby versus prophylactic CPS.

(Am J Cardiol 1992;69:19F–21F)

Several factors have been associated with high-risk percutaneous transluminal coronary angioplasty (PTCA), including left main artery dilation, poor left ventricular function, and dilation of the only patent coronary artery. Nevertheless, research indicates that coronary angioplasty is an acceptable method of coronary revascularization in selected potentially high-risk surgical patients, although complications are higher compared with those seen in angioplasty patients who have normal cardiac function.[1]

Several new devices have been used to support coronary or systemic circulation during high-risk PTCA procedures. These include transcatheter infusion of blood substitutes, prophylactic use of the intra-aortic balloon pump, and reperfusion catheters.[2] Recently, the technique of partial cardiopulmonary support (CPS) or "supported angioplasty" has been developed to reduce the problems associated with high-risk angioplasty and aortic valvuloplasty.[3,4]

Femoral arterial venous cardiopulmonary bypass has been widely used for both elective and emergent open heart surgery.[5] Cardiopulmonary support technology differs from traditional cardiopulmonary bypass systems in that a centrifugal pump, rather than a gravity-fill system, is used to aspirate blood from the central venous pool. Systemic flow rates of 4–6 liters/min can be obtained using 18–20 French cannulae. These large-diameter cannulae can be inserted percutaneously using a sequential dilating technique. In contrast to the intra-aortic balloon pump, output is independent of intrinsic cardiac function and rhythm.[6] Patients require iliac angiography before insertion of the cannulae to ascertain whether any tortuosity or stenosis is present.[7–9] Studies have shown that CPS can be used safely in selected high-risk patients undergoing PTCA and in patients in whom coronary bypass is not feasible, thereby expanding the application of PTCA.[8–10]

In 1988, after initial success with the procedure, 14 institutions formed a National Registry of elective supported angioplasty to document the initial multicenter experience with the procedure (Table I).[6] Investigators demonstrated earlier that CPS is

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TABLE I 1989 National Registry of Elective Supported Angioplasty

Institution	Investigator
University of Maryland,* Baltimore	Robert Vogel, MD
Washington Adventist Hospital, Takoma Park, MD	Fayaz Shawl, MD
William Beaumont Hospital, Royal Oak, MI	William O'Neill, MD
Methodist Hospital, Lubbock, TX	Paul Overlie, MD
Shadyside Hospital, Pittsburgh, PA	James O'Toole, MD
St. Louis University Hospital, St. Louis, MO	Michael Vandormael, MD
University of Michigan Hospital, Ann Arbor, MI	Eric Topol, MD
San Jose Hospital, San Jose, CA	K. Kam Tabari, MD
Goleta Valley Community Hospital, Santa Barbara, CA	John Vogel, MD
Sharp Memorial Hospital, San Diego, CA	Sidney Smith, Jr, MD
St. Francis Cabrini Hospital, Alexandria, LA	Robert Freedman, Jr, MD
Oschner Foundation Hospital, New Orleans, LA	Christopher White, MD
Riverside Hospital, Columbus, OH	Barry George, MD
Scripps Clinic, La Jolla, CA	Paul Teirstein, MD

*Coordination Center.

TABLE II Baseline Characteristics

	Prophylactic CPS (n = 258)	Standby CPS (n = 98)	p Value
Age > 75 years	37 (14%)	20 (20%)	NS
Female	57 (22%)	31 (32%)	NS
Lesions dilated per patient	1.68	1.62	NS
Unprotected left main dilated	20 (8%)	6 (6%)	NS
Only patent vessel dilated	63 (24%)	16 (16%)	NS
LVEF (mean ± SD)	27.7 ± 12.1	34.1 ± 14.9	<0.01
LVEF <25%	109 (42%)	28 (29%)	<0.05

CPS = cardiopulmonary support; LVEF = left ventricular ejection fraction; NS = difference not significant; SD = standard deviation of the mean.

a valuable addition to high-risk coronary angioplasty and aortic valvuloplasty.[4] During the first year of the National Registry, 14 centers enrolled 105 high-risk patients undergoing PTCA.

Inclusion criteria were (1) the presence of severe or unstable angina pectoris, (2) at least 1 likely dilatable coronary stenosis, and (3) left ventricular ejection fraction of <25% or a target vessel supplying >50% of the viable myocardium, or both. Patients who had unstable hemodynamics were considered emergent and were excluded from the registry.

Successful balloon dilation was achieved in 173 (95%) of 182 vessels that underwent attempted dilation. Despite this high success rate, complications were frequent, with 39% of patients experiencing a complication. Blood loss requiring transfusion occurred in 45 patients (43%). More than 50% of the complications involved arterial, venous, or nerve injury at the femoral cannulation site. None of the patients was found to be CPS-dependent after angioplasty, although 1 of the 105 patients required temporary intra-aortic balloon pump assistance; this patient had a successful outcome. Eight patients (7.6%) died during hospitalization, from 2 hours to 7 days after the procedure. Left main coronary artery stenosis was present in 4 of the 8 patients who died, all of whom were ≥75 years old.

The registry's initial experience suggested that high-risk patients who have severely depressed ejection fractions or a single patent coronary vessel and those deemed surgically inoperable can undergo elective angioplasty using CPS with expectations of a good short-term outcome. However, morbidity, particularly with respect to femoral access site complications, was high.[6]

With greater experience, registry members found the time required for percutaneous cannula insertion and initiation of cardiopulmonary bypass decreased to <5 minutes, particularly if contralateral femoral access was previously obtained with small diameter sheaths. In light of the morbidity associated with CPS, it seemed reasonable to place some high-risk patients on "standby CPS." Patients undergoing angioplasty with standby CPS are prepared for the emergency use of CPS, but cardiopulmonary bypass is initiated only if the patient demonstrates irreversible hemodynamic compromise. The approach usually employs arteriographic evaluation of the iliac and femoral vessels, placement of 5 French sheaths in the contralateral femoral vein and artery, and cardiopulmonary system priming. These measures allow full cardiopulmonary bypass to be initiated within a few minutes if hemodynamic collapse occurs.[6]

The 1989 CPS registry enrolled 258 patients undergoing prophylactic CPS and 98 patients who had standby CPS (Table II).[7] Standby CPS provided excellent support for high-risk PTCA. Patients receiving prophylactic and standby CPS had strikingly similar success and major complication rates. Procedural success was seen in 229 patients (89%) in the prophylactic group and in 86 (88%) of the standby group (Table III). Emergency coronary artery bypass graft was needed in 2.3% of the prophylactic group and in 2% of the standby group, and the death rate was 6% in both groups.

There was a trend toward more femoral access site complications and a significant increase in blood transfusions required in patients who had prophylactic CPS (42 vs 17%, p <0.01). There-

TABLE III Procedural Outcome

	Prophylactic CPS (n = 258)	Standby CPS (n = 98)	p Value
Procedural success	229 (89%)	86 (88%)	NS
Major complications			
Q-wave MI	0 (0%)	1 (1%)	NS
EM-CABG	6 (2.3%)	2 (2%)	NS
Death	15 (6%)	6 (6%)	NS
Morbidity			
Femoral complications or transfusion requirement	105 (41%)	12 (12%)	<0.01

CPS = cardiopulmonary support; EM-CABG = emergency coronary artery bypass graft; MI = myocardial infarction; NS = difference not significant.

fore, prophylactic initiation of CPS resulted in increased morbidity and no improvement in outcome compared with standby CPS.

Seven of the 98 patients who had standby CPS had irreversible hemodynamic deterioration during PTCA. Cardiopulmonary support was successfully initiated in all 7 patients, 4 of whom went on to have successful procedures without requiring emergency coronary artery bypass surgery. Of the 2 standby CPS patients undergoing standby CPS who had an emergency bypass surgery, 1 died.

Although this study favored standby CPS over prophylactic CPS, some patient subgroups may still benefit from prophylactic CPS. For example, it is possible that patients who have extremely low ejection fractions (left ventricular ejection fraction <20%) would have better outcomes with prophylactic CPS. Patients who have associated abnormalities such as significant valvular insufficiency might also benefit from prophylactic CPS. Some physicians might also favor prophylactic CPS in patients who have severe left ventricular dysfunction and relatively poor PTCA target lesions (i.e., American College of Cardiology/American Heart Association type B and C lesions) that might require prolonged or multiple dilations.

Prophylactic CPS can cause significant morbidity and is rarely needed, even for high-risk angioplasty patients. Standby is advantageous because CPS can be selectively applied only to those patients who clearly need it, while avoiding the morbidity of CPS in patients in whom it is not essential.

The issues surrounding CPS for high-risk PTCA are controversial. CPS is a technically challenging and expensive procedure associated with significant patient morbidity. Despite its drawbacks, CPS has been shown to help save the lives of selected patients undergoing high-risk procedures. Standby CPS provides excellent support for most high-risk PTCA patients. Further study will better define appropriate patient selection for standby versus prophylactic CPS.

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Complex Angioplasty: A Surgeon's Perspective

Robert H. Jones, MD

Surgeons commonly have reacted with skepticism to the introduction of catheter-based interventional approaches to treating coronary artery disease, prompted apparently, by a desire to protect what had been exclusively their turf. Reasonable surgeons now largely accept the concept of nonoperative mechanical treatment of coronary heart disease, and their constructive criticisms regarding amelioration of coronary anatomy without thoracotomy remains valuable. The value of catheter-based techniques compared with operative or noninterventional treatment has not been defined in many clinical settings. The complexity of evaluating these rival technologies increases as the complexity of cases progresses from simple 1-vessel disease to more extensive coronary artery disease. Ongoing randomized trials may help define indications for these procedures, but patients entering these trials represent a highly select subset. Therefore, applications to broader patient populations will likely require analysis of observational data. Newer catheter-based technologies introduce modes of injury to the coronary arterial system that have not been encountered previously in medical practice. As technologies evolve, decisions about the need for operative intervention become increasingly complex. In the many clinical settings resulting from efforts to improve angioplasty, optimal patient care occurs in environments with good communication and cooperation between all physicians involved in interventional treatment of coronary artery disease.

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The use of percutaneous transluminal coronary angioplasty (PTCA) has grown rapidly within the past decade as a primary treatment for coronary atherosclerotic heart disease. In experienced hands, PTCA has a high rate of initial success (angina relief) and a low rate of complications.[1] The procedure is particularly useful to treat patients with 1-vessel disease whose outlook without coronary artery bypass surgery (CABG) is good and for patients with acute myocardial infarction who need rapid restoration of coronary blood flow to minimize myocardial infarct size.[1]

Despite the growing role of the procedure, the technique is not free from mortality or morbidity.[2] Arterial dilation is not possible or is complicated by further arterial narrowing or occlusion in a small percentage of patients in whom PTCA is undertaken.[1] A failed procedure necessitating CABG accounts for a significant proportion of the complications.[2] Several groups of investigators have reviewed early results of CABG for unsuccessful PTCA, and, in these series, the risk of perioperative myocardial infarction ranges from 21 to 58%.[1]

Surgeons have commonly reacted with skepticism and hostility to the introduction of catheter-based interventional approaches to treating coronary artery disease. This reaction was prompted by a desire to protect what had been their exclusive turf. Reasonable surgeons now have largely accepted the concept of nonoperative mechanical treatment of coronary heart disease. Still, they remain a valuable resource for constructive criticism regarding altering coronary anatomy without opening the chest.

In many clinical settings, the value of catheter-based techniques compared with operative or noninterventional treatment has not been defined. The complexity of evaluating these rival technologies increases in the progression from simple 1-vessel disease to more complex, extensive coronary artery disease. Ongoing randomized trials may help define indications for these procedures, but patients entering these trials represent a highly select subset. Therefore, applications to broader patient populations will likely require analysis of observational data.

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IMPLICATIONS OF FAILED PTCA

Although new interventional technologies have broadened the population of patients who are amenable to catheter-based techniques, the technologies have not improved the results of standard angioplasty. About 8–10% of attempted angioplasties are unsuccessful in dilating the narrowed arterial segment or sustaining its patency.[3] Of these attempts, half of the failures are due to an inability to cross the stenosis with the angioplasty wire or balloon or to dilate the stenosis, even though the balloon is positioned appropriately. The other half are due to abrupt closure of the artery after dilation.[4] Commonly, abrupt closure is accompanied by chest discomfort and electrocardiographic evidence of ischemia and requires urgent revascularization (repeat PTCA or emergency CABG) of the occluded vessel to prevent or limit myocardial necrosis. This, in turn, can prevent or limit myocardial injury.[3] In our experience, abrupt closure is a good indication for immediate surgery. The patient can be treated medically before transfer to the operating room, or it may be feasible to insert a balloon in the interim. In some cases, bailout devices may be used, but such intervention should be kept to a minimum because of the potential risks they pose to the patient.

Emerging strategies for failed PTCA that show promise include the autoperfusion dilation catheter, the endoluminal stent, laser "welding" of the dissected intimal segment, and the Simpson atherectomy device. Another promising indirect intervention is percutaneous femoral–femoral cardiopulmonary bypass.[5]

Nevertheless, the high-risk patient will remain at high risk no matter what new strategy is selected. Some investigators also argue that none of the strategies under development is likely to obviate the absolute requirement for backup, emergency surgical revascularization.[6]

In the initial National Heart, Lung, and Blood Institute PTCA Registry, acute closure accounted for 53% of emergency coronary artery bypass operations, 28% of inhospital deaths, and 36% of myocardial infarctions following PTCA.[7] Of patients with abrupt closure, 5.3% died and 75% underwent emergency coronary artery revascularization or had a myocardial infarction.[7] A review of the literature indicates that emergency CABG after failed PTCA is associated with a significant increase in morbidity and mortality, increased length of stay, and increased use of resources and personnel with, consequently, increased financial effect.[8] In addition, the data suggest that it is inappropriate to equate emergency CABG after a failed PTCA with elective CABG.[8]

TABLE I Bypass/Angioplasty Trials

Angioplasty Compared to Optimal Drug Therapy (ACME)
Bypass Angioplasty Revascularization Investigation (BARI)
Coronary Angioplasty vs. Bypass Revascularization Investigation (CABRI)
Emory Angioplasty versus Surgery Trial (EAST)
German Angioplasty Bypass Investigation (GABI)
Randomized Intervention Treatment of Angina (RITA)

OUTCOME COMPARISON OF CABG AND PTCA

Differences in late clinical outcome for CABG and PTCA have been documented in the literature.[1] Connor and colleagues[1] have reported that patient survival and freedom from myocardial infarction during the first 5 years after the procedures are similarly good for CABG and PTCA; however, risks of recurrent angina pectoris and need for an additional revascularization procedure appear to be substantially greater for patients who have had PTCA than for those who have had CABG.

Several bypass/angioplasty trials are under way nationally to compare outcomes with PTCA and CABG (Table I). Preliminary data from the Bypass Angioplasty Revascularization Investigation (BARI) trial have documented an increasing use of catheter-based techniques in patients with complex coronary anatomy, especially those with prior coronary artery bypass grafting. The future direction of angioplasty appears certain to include a population of very high-risk patients who may not be candidates for surgery if catheter-based techniques fail acutely. However, in most settings, the major role of the surgeon in supporting development of angioplasty is to provide emergency surgery for this new form of cardiac injury.

CONCLUSION

Newer catheter-based technologies introduce modes of injury to the coronary arterial system not encountered previously in medical practice. As technologies evolve, decisions about the need for operative intervention become increasingly complex. Arterial injuries without occlusion or free hemorrhage, such as may occur from a perforation by an atherectomy extraction device in a patient without prior bypass, can be treated with careful observation, including repeat catheterization. In the many clinical situations that result from efforts to improve angioplasty, optimal patient care occurs in environments that have good communication and cooperation between all physicians involved in

interventional treatment of coronary artery disease.

Greater attention must also be focused on physiologic end points when determining whether a patient actually needs PTCA. Many of those who undergo PTCA are not ischemic and do not need to have their vessels dilated. At the same time, PTCA can be an extremely beneficial procedure in persons who have poor cardiovascular physiology, including those in whom revascularization can raise exercise ejection fractions and restore normal heart function.

It behooves all cardiologists to give careful consideration to the selection of patients for any interventional procedure before catheterization. At that time, determinations can be made on graft placement or when interventional devices such as balloons, stents, or lasers can be used to restore the heart to as normal a condition as possible.

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Changing Trends for Surgical Standby in Patients Undergoing Percutaneous Transluminal Coronary Angioplasty

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In 1988 the American College of Cardiology/American Heart Association (ACC/AHA) task force subcommittee on Guidelines for Percutaneous Transluminal Coronary Angioplasty (PTCA) recommended that an experienced cardiovascular surgical team be available within the institution for emergency surgery for all angioplasty procedures. The subcommittee felt strongly that this requirement allowed for no exception, stating that it could not condone existing arrangements that required the transportation of patients to off-site surgical facilities for emergency cardiac surgery. Such arrangements failed to meet the necessary standards of care exercised by prudent physicians. Interventional cardiologists are recognizing that it may be prudent for the ACC/AHA task force to revise its 1988 guidelines. Improved operator technique and new technologic advances, such as lasers, atherectomy devices, stents, and perfusion pumps and balloons, have helped extend the reach of PTCA to more seriously ill patients. With new technologies for angioplasty and an increased awareness of risk factors, active standby can be markedly reduced, thereby resulting in enormous cost reductions and in more appropriate patient care.

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Within the past decade, percutaneous transluminal coronary angioplasty (PTCA) has been used to treat hundreds of thousands of patients with widening indications, increasing success rates, and low complication rates.[1] Improved operator technique and new technologic advances, such as lasers, atherectomy devices, stents, and perfusion pumps and balloons have helped extend the reach of PTCA to more seriously ill patients. Interventionalists are recognizing that increased success rates mean active surgical standby is no longer automatically necessary. Thus, it may be prudent for the American College of Cardiology/American Heart Association (ACC/AHA) task force subcommittee on Guidelines for Percutaneous Transluminal Coronary Angioplasty to revise its 1988 guidelines.

The guidelines recommend that an experienced cardiovascular surgical team be available within the institution for emergency surgery for all angioplasty procedures.[2] The subcommittee felt strongly that there should be no exception to this requirement and stated that "all arrangements requiring the transportation of patients to offsite surgical facilities for such emergency surgery fail to meet the necessary standards of care exercised by prudent physicians and therefore cannot be condoned."[2] The guidelines further state that although surgical standby arrangements vary from institution to institution depending on the number of operating rooms available for cardiac surgery and the number of surgeons, perfusionists, nurses, and other personnel, the most essential requirement is the capacity to provide rapid surgical support when angioplasty fails. Otherwise, the subcommittee said, patient care becomes compromised.[2]

As operators gain experience with PTCA and increase their understanding of preprocedural factors, the task force's position on surgical standby should be reexamined. Investigators have identi-

TABLE I Characteristics of Type A Lesions

Type A Lesions*	Characteristics
Discrete (< 10 mm length)	Little or no calcification
Concentric	Less than totally occlusive
Readily accessible	Not ostial in location
Nonangulated segment, < 45°	No major branch involvement
Smooth contour	Absence of thrombus

*High success, 85%, and low risk.
Adapted from *J Am Coll Cardiol.*[2]

TABLE II Characteristics of Type B Lesions

Type B Lesions*	Characteristics
Tubular (10–20 mm length)	Moderate to heavy calcification
Eccentric	Total occlusion < 3 months old
Moderate tortuosity of proximal segment	Ostial in location
Moderately angulated segment, > 45°, < 90°	Bifurcation lesions requiring double guide wires
Irregular contour	Some thrombi present

*Moderate success, 60–85%, and mocerate risk.
Adapted from *J Am Coll Cardiol.*[2]

TABLE III Characteristics of Type C Lesions

Type C Lesions*	Characteristics
Diffuse (> 2 cm length)	Total occlusion > 3 months old
Excessive tortuosity of proximal segment	Inability to protect major side branches
Extremely angulated segments, > 90°	Degenerated vein grafts with friable lesions

*Low success, 60%, and high risk.
Adapted from *J Am Coll Cardiol.*[2]

fied certain patient characteristics associated with risk from coronary angioplasty, including advanced age, female gender, congestive heart failure, unstable angina, multivessel coronary disease, and morphologic findings.[3] For example, stenosis characteristics that predispose patients to complications include long stenoses, stenoses at points of vessel angulation or branching, thrombus, diffuse disease, and high-grade stenosis. Lesion morphology, left ventricle function, and extent of disease are also important factors in predicting risk.[3]

Type A lesions are considered to have low risk of abrupt vessel closure with an anticipated success rate of ≥85%; type B lesions characteristically result in a lower than optimal success rate, in the range of 60–85% or have a moderate risk of abrupt vessel closure, or both; and type C lesions characteristically result in a low success rate (<60%) or have a high risk of abrupt closure, or both (Tables I–III).[3] Thus, operators should be fairly confident that they can do a reasonably good job at low risk with type A lesions, but type C lesions may require an alternative strategy to PTCA.

Several investigators are attempting to improve their technique to reduce patient risk during PTCA and to achieve the maximum improvement in arterial luminal diameter possible with a minimum of vessel disruption. Hartzler's group[4] found that PTCA of coronary stenoses can be achieved with high success rates and low complication rates when graded inflations to pressures just sufficient to achieve full balloon expansion are performed. The investigators concluded that most coronary lesions can be dilated at inflation pressures below 10 atm. Such findings may have implications for new balloon and nonballoon technologies under development. Although specialty balloons permitting high inflation pressures may be needed on rare occasions, most stenoses can be successfully dilated with pressures obtainable with current catheters. Several new nonballoon technologies currently under investigation, such as coronary excimer laser therapy and atherectomy, may prove to have a role in lesions not readily dilated with conventional balloon catheters.[4]

In a recent study by Spielberg et al,[5] the investigators assessed complication rates of 4 coronary angioplasty regimens differing with respect to catheter material and adjuvant medication. In group 1, PTCA was performed with steerable, partially Teflon-coated guide wires and conventional dilation catheters with polyvinyl chloride balloons or polyethylene balloons. In group 2, PTCA was performed with monorail dilation catheters and partially Teflon-coated guide wires. Group 3 had the same technique and material as in group 2, but urokinase was infused during the intervention; and group 4 employed PTCA with monorail dilation catheters and fully silicon-coated guide wires.

The incidence of intermittent or recurrent occlusions during PTCA increased significantly ($p = 0.04$) from group 1 (conventional steerable systems) to group 2 (monorail technique). The further increase in the incidence of these complications in group 3 (monorail technique with urokinase) was not statistically significant. In group 4 (fully silicon-coated guide wires, no urokinase), the rate of intermittent or recurrent occlusions was as low as it was in group 1.[5]

The study found that urokinase did not prevent intracoronary thrombus formation with the monorail technique, and the authors suspected that in the case of PTCA-induced regional intimal dissection, fibrinolysis can prevent reestablishment of intima adherence to the vessel wall (Table IV). The investigators concluded that urokinase in PTCA is a potentially harmful regimen and suggest

that the monorail technique be performed with fully silicon-coated guide wires and without urokinase.[5]

As operator experience and angioplasty equipment have evolved, many centers have liberalized the selection criteria to include patients with significant stenoses in multiple coronary arteries. In another study by Hartzler and colleagues,[6] the investigators found that multivessel coronary angioplasty was safe and effective and resulted in excellent long-term symptom relief and survival. The study included 3,186 patients who had coronary angioplasty of 2 (2,399 patients) or 3 (787 patients) of the 3 major epicardial coronary systems. Angiographic success was achieved in 10,836 (96%) of 11,336 lesions with attempted dilation. Complete revascularization was achieved in 1,835 patients (58%). Serious complications, including acute infarction, emergency surgery or death, occurred in 94 patients (2.9%) (Table V). Emergency coronary artery bypass grafts (CABG) were required in only 1% of patients. Thus, these complications were encountered infrequently with multivessel angioplasty and at rates similar to those seen with single vessel angioplasty.[6]

Until recently, relatively few patients were considered candidates for coronary angioplasty when symptoms recurred after prior coronary bypass surgery.[7] However, recent investigations show a more salutary trend, and patients with prior bypass surgery now represent a major group in which angioplasty is utilized.[8]

In a study to assess outcome when angioplasty is performed on patients with prior CABG, PTCA was shown to be successful in 356 (84%) of the 422 patients and in 475 (84%) of 563 vessels attempted (Figure 1).[8] Ten patients (2.4%) underwent emergency CABG and 13 (3.1%) had Q-wave myocardial infarction. The study demonstrated that coronary angioplasty can be performed with a high initial success rate, low morbidity, and very low mortality in patients with prior coronary bypass surgery, although restenosis, particularly of vein grafts, remains a problem. Initial risk and late survival in selected patients who had prior surgery compare favorably with reports of reoperation, but recurrence of stenosis after angioplasty significantly compromises event-free survival. Satisfactory long-term results are more likely when PTCA is directed at native vessels, newer vein grafts, distal anatomic sites, or internal mammary artery grafts.[8]

Although research on coronary angioplasty in young adults (<40 years) is limited, a study by Webb and colleagues[9] found that PTCA among

TABLE IV Acute Complications of PTCA of 725 Lesions in 660 Patients*

	Group 1 (n = 192)	Group 2 (n = 91)	Group 3 (n = 232)	Group 4 (n = 210)
Intermittent occlusions	3 (1.6)	7 (7.7)	19 (8.2)	7 (3.3)
Recurrent occlusions	2 (1.0)	0	5 (2.2)	1 (0.5)
Permanent occlusions	7 (3.6)	8 (8.8)	24 (10.3)	4 (1.9)
Occlusion of side branch	4 (2.1)	5 (5.5)	8 (3.4)	6 (2.9)
Coronary thrombus	5 (2.6)	5 (5.5)	15 (6.5)	2 (1.0)
Emergency CABG	1 (0.5)	2 (2.2)	5 (2.1)	1 (0.5)
PTCA-related death	1 (0.5)	1 (1.1)	5 (2.1)	1 (0.5)
No. patients with ≥1 complication	17 (9.6)	16 (20)	49 (23)	19 (9.8)

*In parentheses is the percentage of complications relative to all lesions treated within each group.
CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty.
Adapted from *Cathet Cardiovasc Diagn.*[5]

TABLE V In-Hospital Complications: Single Versus Multivessel Angioplasty

	SV PTCA (n = 4,543)		MV PTCA (n = 3,186)		
	No.	%	No.	%	p Value
Infarction	75	1.7	47	1.5	NS
Urgent CABG	95	2.1	33	1.0	0.002
Death	40	0.9	31	1.0	NS

CABG = coronary artery bypass graft surgery; MV = elective multivessel; NS = difference not significant; PCTA = percutaneous transluminal coronary angioplasty; SV = elective single vessel.
Adapted from *J Am Coll Cardiol.*[6]

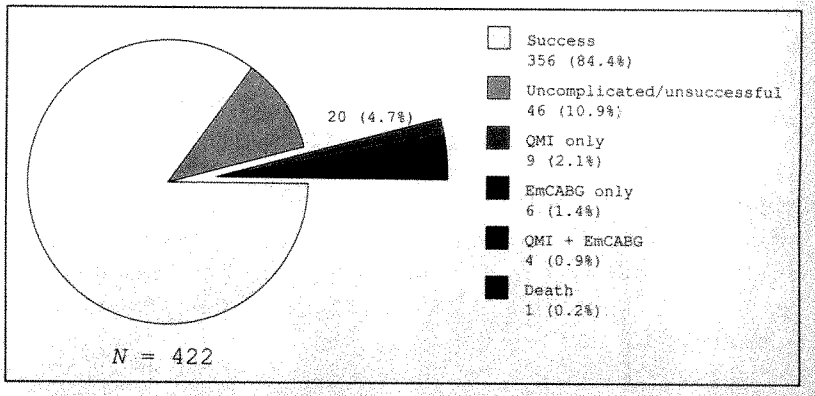


FIGURE 1. Major cardiac events. EmCABG = emergency coronary bypass graft surgery; QMI = Q-wave myocardial infarction. (Reprinted with permission from *J Am Coll Cardiol.*[8])

TABLE VI Percutaneous Transluminal Coronary Angioplasty Demographics

PTCA patients < 40 years old
148 patients
Success, 90.5%
SV PTCA, 70%; MV PTCA, 30%
Complications, 2%
Emergency CABG, 0.7% (1 patient)
Nonfatal MI, 0.7% (1 patient)
Fatal MI, 0.7% (1 patient)

CABG = coronary artery bypass graft surgery; MI = myocardial infarction; MV = elective multivessel angioplasty; PTCA = percutaneous transluminal angioplasty; SV = elective single vessel angioplasty.
Adapted from *J Am Coll Cardiol.*[9]

patients in this category has a high likelihood of success, with low morbidity and mortality. In the study of 148 patients, PTCA was performed on a single vessel in 70% of patients and on multiple vessels in 30%; it was performed on a totally occluded vessel in 20%. The procedure was successful in 90.5% of patients, unsuccessful but uncomplicated in 7.4%, and complicated by myocardial infarction in 0.7%. Emergency bypass surgery was needed in 0.7%, and death occurred in 0.7% (Table VI).

At late follow-up (mean 3.7 ± 3 years; range 0.5–11.5 years) after successful PTCA, 94% of patients were alive, 79% were free of angina, and 85% had returned to work; late myocardial infarction occurred in 4%. Actuarial survival at 5 years was 95%, and 85% of patients were free from death, infarction, or bypass surgery. A second PTCA was performed in 29 patients (22%) and was successful in 27 (93%), with no deaths. Elective coronary bypass surgery was performed in 8.5% of patients, with perioperative infarction in 9% and no deaths. By univariate analysis, late death was more likely to occur in hypertensive and diabetic patients. Thus, early and late results after PTCA in young adults are favorable, but certain risk factors are important predictors of outcome. The investigators found that late revascularization procedures for restenosis or disease progression were common.[9]

Most patients undergoing coronary angioplasty after prior coronary bypass surgery do not require reoperation.[10] In a study that examined outcome in 46 patients with a history of CABG followed by failed elective PTCA necessitating urgent reoperative CABG, investigators concluded that most patients survive the procedure, but the incidence of myocardial infarction is high in those with acute ischemia at operation. Still, patients who leave the hospital can look forward to favorable event-free survival over the first several years. They also noted that overall risk may be modified, depending on detailed consideration of the severity and distribution of the coronary and native vessel disease, and the expertise and experience of the coronary angioplasty operator, cardiac anesthesiologists, and cardiothoracic surgeon.[10]

Other studies point to increasing success rates for coronary angioplasty in complex and potentially high-risk conditions. In an analysis of the short- and long-term effects of coronary angioplasty in 61 patients with severely depressed left ventricular function (ejection fraction ≤35%) with unstable or refractory anginal symptoms, or both, in whom revascularization was necessary despite increased risk, investigators concluded that coronary angioplasty can be performed with a short-term success rate comparable to that of routine angioplasty or surgical procedures.[11]

The 61 patients in the study group had a relatively high periprocedural mortality rate despite a good initial success rate; in addition, the high follow-up mortality rate may be a manifestation of restenosis overlying a severely compromised myocardium. Coronary angioplasty in such patients can be performed with a high degree of immediate success but may not affect the natural history of these patients, particularly the late mortality rate. However, early detection of silent restenosis may be possible by elective repeat angiography or nuclear perfusion imaging, or both, which could lead to timely repeat angioplasty and perhaps fewer late deaths. The study did not demonstrate angioplasty to be a better method of revascularization than bypass surgery. Rather, it is a reasonable and potentially feasible alternative. Further investigation is necessary to determine subgroups that may be preferentially treated by one or the other therapy.[11]

SURGICAL STANDBY: THE ISSUES

Failure of PTCA resulting in emergent or elective CABG surgery has been noted since the initial report of the procedure.[12] In the 169 patients of Gruentzig treated in Zurich,[13] 18% had CABG surgery within 1 month of their hospitalization; of these, 7.7% received it as an emergency procedure. Currently, many centers report emergency rates in the 2% range.[12] Although there has been an enormous explosion of new technology, few data are available on current practice patterns for surgical standby for PTCA. In view of the time commitments and cost involved for surgical standby, my colleagues and I conducted three surveys to characterize practice patterns in the United States and abroad. During 1990, we conducted surveys of

TABLE VII Surveys of PTCA Experience

	Geneva (Europe, Canada, Mexico)	Emory (USA)	Santa Barbara (USA)
No. countries/states	13	31	19
Average no. PTCA/yr	391	80	183
% <100/yr	8%	64%	39%
Average experience/yr	5.2	4.7	6.6
No. responses	24	75	31
Average no. ORs	3.0	2.3	3.6

OR = operating room; PTCA = percutaneous transluminal coronary angioplasty.

TABLE VIII Estimated Cost for Standby 1990—US

270,595	No. patients
$990.00	(cost/1 hour)
$267,889,050.00	Patient costs

($156,945,100.00 estimated actual hospital costs)
Does not include
- Surgeon, anesthesiologist fees
- Packs not opened
- Pump not set up

Assume 2.0% emergency CABG
Cost per patient → CABG, $49,499.00

CABG = coronary artery bypass graft surgery.

practice patterns of interventional cardiologists attending angioplasty courses at Emory University, Atlanta; in Geneva, Switzerland; and at the American College of Cardiology workshop on interventional cardiology in Santa Barbara.

A demographic analysis of operator experience with PTCA showed that experience varied widely among the three survey groups. The European group, which represented 13 countries, was the most experienced, with an operator average of approximately 391 PTCAs annually. The Santa Barbara group (representing 19 states) performed about 200, and the Emory group (31 states) performed about 80 (Table VII).

The survey found that approximately 86% of PTCA cases were elective and 14% were emergency. While 95.9% of cardiologists at the Emory course and 81% at the Santa Barbara workshop used routine standby when performing elective PTCA, only 72% of the European contingent reported it. Thus, in 1990 an estimated 270,595 patients undergoing PTCA in the United States had surgical standby. At an estimated patient cost of $990 at Goleta Valley Community Hospital (Santa Barbara, California), excluding physician fees and no pump set up or packs opened, an estimated nationwide surgical standby patient cost during 1990 was $267,889,050. This is a cost of approximately $50,000 per patient going to emergency bypass, assuming a 2% rate (Table VIII). If one adds the projected professional fees, the cost approaches $100,000 per patient undergoing emergency CABG. If the emergency rate were 1%, the cost would be $200,000.

When asked if the cost of standby was an important issue, 75–80% of participants in the US surveys answered yes, as compared with fewer than 50% of the Geneva group. When participants were asked if they knew the surgeon's cost for standby, however, the percentages dropped dramatically, with only about 30% of the US participants aware of those costs. The percentages continued to decline when participants were asked about their knowledge of anesthesiologists' costs and operating room costs. Fewer than 50% of participants in the US surveys knew the cardiologists' costs for such services (Figure 2).

Several emerging factors suggest that it may be possible to characterize the risk of angioplasty and thus individualize the level of standby. Preproce-

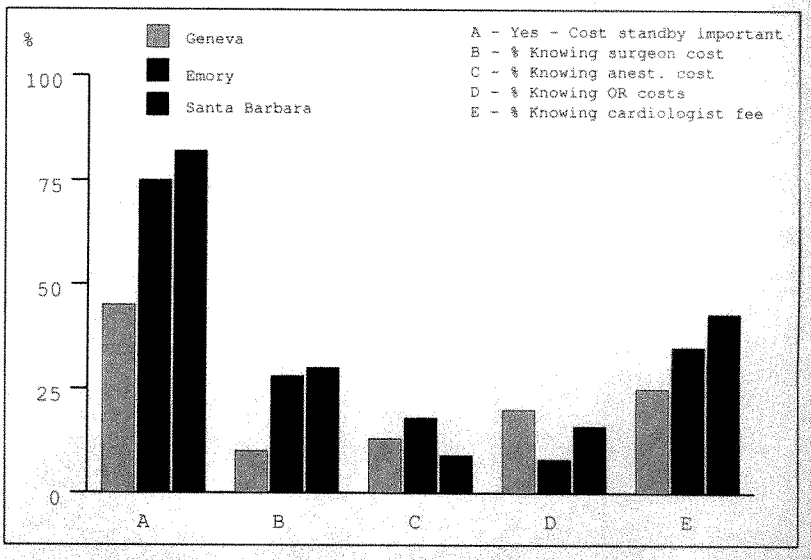


FIGURE 2. Percutaneous transluminal coronary angioplasty surveys: physician cost awareness. anest. = anesthesiologist; OR = operating room.

TABLE IX Hospitals Without Surgical Backup

	%	Distance to Backup
Geneva	41%	8–60 km 10–60 min, by ambulance, helicopter
Emory	6%	60–150 miles, 30 min by helicopter
Santa Barbara	22%	2–30 miles, 15–20 min

TABLE X Active Standby, Operating Room Open, Surgeon Available

Proximal LAD
LV dysfunction, EF <40%
Vessel → major blood supply
Closure → shock
Dominant RCA, circulation
"Last" vessel
Multivessel angioplasty
Non-MI vessel in AMI, SVG with occluded native vessel
Left main equivalent or unprotected left main
Anyone would operate if failed PTCA
B_2, C lesions

AMI = acute myocardial infarction; EF = ejection fraction; LAD = left anterior descending coronary artery; LV = left ventricular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; SVG = saphenous vein graft.

dural factors, such as unstable angina, diabetes, gender, and age, influence risk as do anatomic variables such as left ventricular function, lesion morphology, the extent of vessel involvement, vessel size, and lesion site. Intraprocedural factors such as equipment used, device used, perfusion techniques, and inflation techniques may also affect success.

Numerous therapies have evolved to decrease myocardial ischemia and failed angioplasty. These include local coronary defensive measures (including stents, autoperfusion and active perfusion, atherectomy devices, and laser balloon angioplasty) and systemic support (including cardiopulmonary support (CPS), and intra-aortic balloon pumping). Given the availability of stents and CPS, the surveys indicated that many physicians would be willing to consider PTCA without active surgical standby. When participants were asked if they would consider PTCA without standby given the availability of stents, cardiopulmonary support, autoperfusion, directional atherectomy, intra-aortic pump balloon, or laser balloon angioplasty, all three groups showed the highest receptivity to stents and CPS (Figure 3). CPS was more widely accepted among the American physicians than those in the European group, and among all three survey groups directional atherectomy and the intra-aortic pump were considered by <25%. These reports indicate that the availability of these technologies, as well as responsiveness to the risk of pre- and intraprocedural factors, may alter practice patterns.

Despite the recommendations of the ACC/AHA task force subcommittee on Guidelines for Percutaneous Transluminal Coronary Angioplasty, the surveys indicate that the practice of PTCA in hospitals without on-site surgical backup is widespread in some areas. Findings from the European survey showed that 41% of respondents reported that their hospitals did not have surgical backup. Hospitals were located 8–60 km (1–36 miles) from the backup hospital, requiring a transport time of 10–60 minutes by ambulance and/or helicopter. In the Emory group, only 6% of physicians reported facilities that did not have backup. Hospitals without backup were located 60–150 miles from the backup hospital, requiring a 30-minute transport time via helicopter. In the Santa Barbara study, 22% of physicians reported facilities that did not

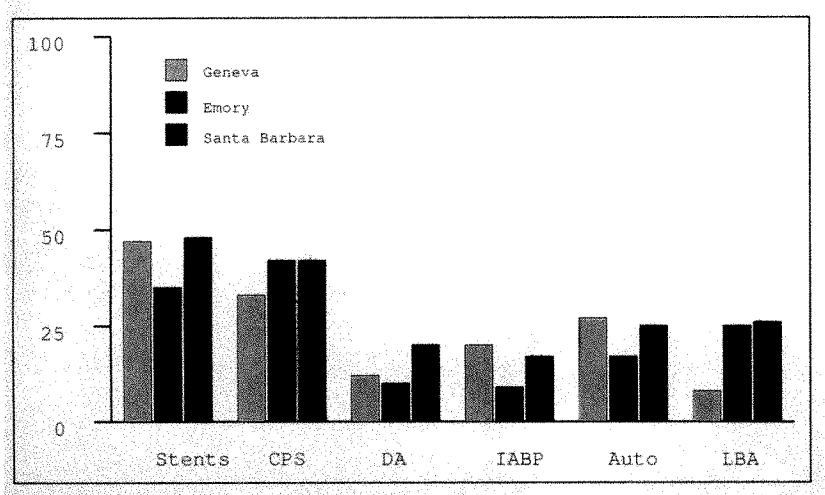


FIGURE 3. Strategies for standby. Consider percutaneous transluminal coronary angioplasty without standby with these procedures.
Auto = autoperfusion;
CPS = cardiopulmonary support;
DA = directional atherectomy;
IABP = intra-aortic pump balloon;
LBA = laser balloon angioplasty.

TABLE XI Passive Standby, Operating Room Not Open, Surgeon Available

Small vessel or midvessel disease
Total occlusion
Infarct vessel, AMI, salvage
Small area at risk, vessel serves scar
Good LV
Branch vessels
Gruentzig vessel
Mid-LAD
Small grafts (not host vessel)
Elderly
Saphenous grafts with stent
Collateral protection

AMI = acute myocardial infarction; LAD = left anterior descending coronary artery; LV = left ventricular.

TABLE XII No Standby, Coronary Artery Bypass Grafting

Patient absolutely refuses, agrees to accept consequences (death)
Surgeon refuses case
Nonsurgical, cancer, COPD
Nondominant RCA
Closure less dangerous than CABG
Total occlusion (RCA) with collateral
Small area at risk, graft-protected RCA

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; RCA = right coronary artery.

have backup; these facilities were located 2–30 miles from the backup hospital and required 15–20 minutes of transport time (Table IX).

Anecdotal information from other sources indicates high PTCA success rates without on-site surgical backup. Three large Canadian hospitals perform PTCA without on-site surgical backup with excellent results (Dragatakis LN, Klink P: Personal communications, November 1990). Approximately 50% of surgeries in Germany are performed in hospitals without in-house surgical backup. One German center has performed 5,007 procedures with good results without in-hospital surgical backup.[14] Their emergency CABG rate was 0.2%.

Excellent results have also been reported from Belfast, Ireland, by Richardson and associates.[15] They concluded that with careful selection of patients, coronary angioplasty may be safely performed in a hospital without on-site cardiac surgical facilities, provided that these facilities are available at a nearby center. These centers generally are within 2–3 km (approximately 1–2 miles) of the backup hospital, and special attention is given to patient selection and defensive strategies for threatened or failed angioplasty.

CONCLUSION

Addressing the problem of failed PTCA is critical to resolving the debate about surgical standby. Physicians must be able to deal with myocardial ischemia, myocardial infarction, and stabilizing patients before CABG or before continuing with medical therapy. Strategies that physicians may consider to avoid PTCA failure include staging procedures in certain persons, avoiding worrisome lesions, and avoiding the procedure in patients with ischemia and clot formation. Technologic developments such as the stent and perfusion techniques will be increasingly important tools to prevent ischemia and stabilize the patient.

With new technologies for angioplasty and an increased awareness of risk factors, active standby can be markedly reduced, thereby resulting in enormous cost reductions and wasted hours. As of January 1, 1991, Medicare payment for Diagnostic Related Group 112 for PTCA was $7,751.32 in the Santa Barbara area. Using one balloon catheter only, actual out-of-pocket costs to the hospital were approximately $7,000. The Diagnostic Related Group (DRG) payment does not include additional provisions for the cost of special devices, lytic agents, special solutions, CPS, or surgical standby.

Thus, practicing interventional cardiologists must carefully address the indications for surgical standby—the prevention of ischemia during PTCA—when making decisions about the most appropriate care for their patients. A close analysis of the prudent use of technology is essential if we expect to have the continuing privilege of providing the best technology for our patients. It is recommended that the guidelines for PTCA be revised. I would suggest the following levels of standby:

- active—operating room is open and ready and surgeon is available
- passive—next operating room and surgeon available, and
- no standby.

Patients who might be appropriate candidates for these strategies are described in Tables X–XII.

In addition, one must consider the possibility of PTCA in a hospital without on-site surgical backup. It is recognized that facilities are abundant in the United States, and there is little need for elective PTCA in a hospital without on-site surgical backup. However, there is considerable debate as to the role of PTCA in acute myocardial infarction. If PTCA emerges as an important alternative to lytic therapy in some situations, *the performance of PTCA in a hospital without on-site surgical backup may be justified.* The results of Kahn and associates[16] support such a possibility with direct PTCA

in patients with acute myocardial infarction. In addition, recent results of primary angioplasty for acute myocardial infarction *without on-site surgical backup* suggests that appropriate patients can be selected for such procedures. In the Seattle experience, the emergency bypass rate was 1.3% with no deaths.[17] Similar results have been noted by others.[18]

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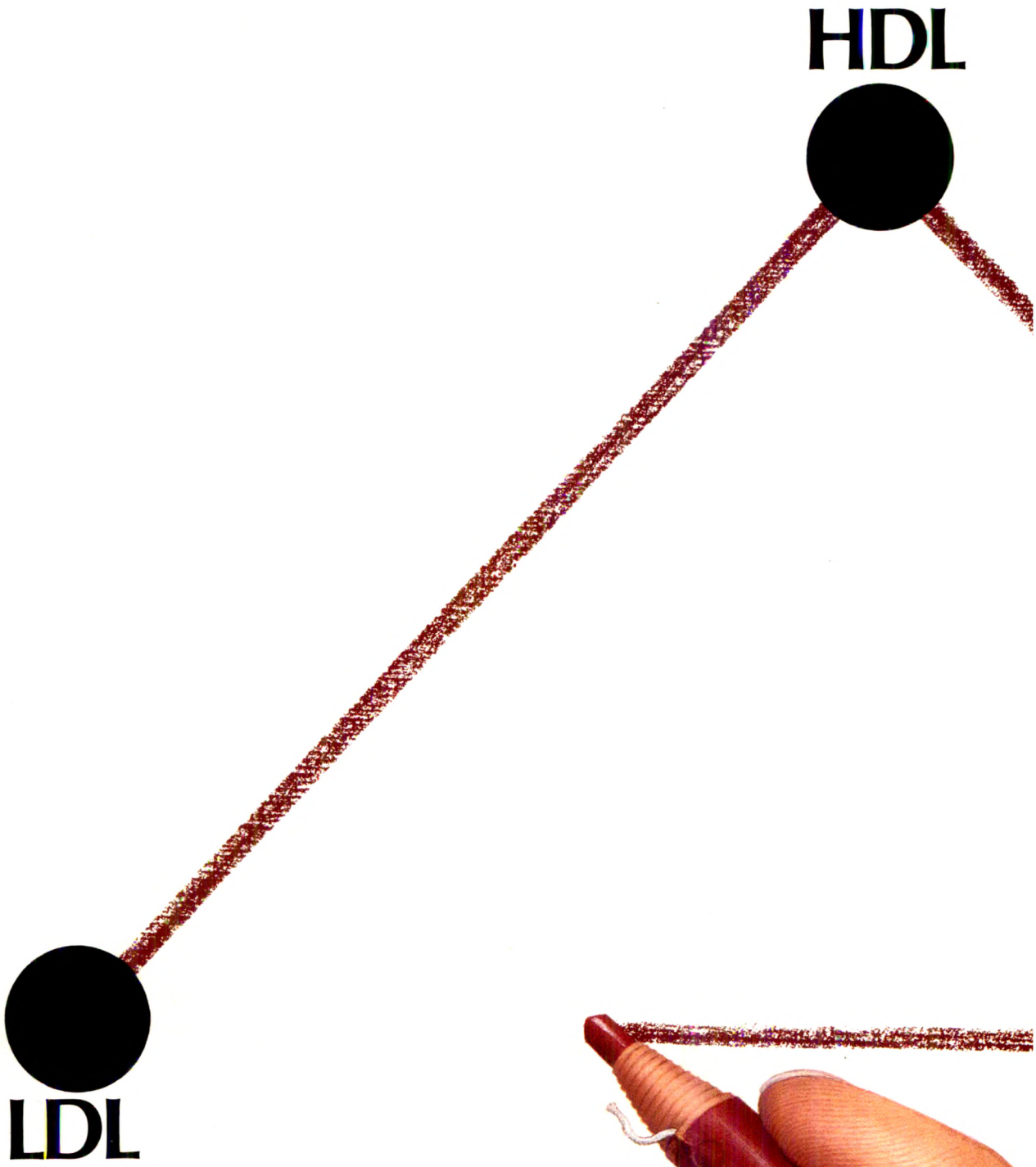
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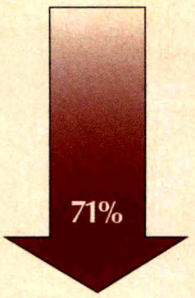
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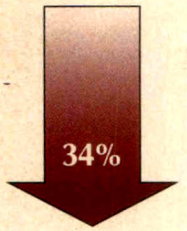
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Reference 1. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study: implications for treatment. *Circulation.* 1992;85:37-45.

*Defined as a combination of definite coronary death and/or definite myocardial infarction.
[†]Mean HDL = 35 mg/dL; mean LDL = 208 mg/dL; P = .005; 95% CI 21.2 to 118.6.

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CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder d sease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lopid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lopid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically-significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lopid group (43 vs 27 patients in the placebo group, p=0.056).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lopid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lopid group and none in the placebo group (p=0.06; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lopid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

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2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lopid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lopid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lopid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lopid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lopid should be discontinued.

4. Concomitant Anticoagulants – Caution should be exercised when anticoagulants are given in conjunction with Lopid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lopid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lopid therapy should be withdrawn.

6. Cataracts – Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy** – Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lopid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy** – Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions** – (A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility** – Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lopid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B** – Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lopid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lopid is tumorigenic in male and female rats, the use of Lopid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers** – Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes** – Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lopid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lopid administration.

8. **Liver Function** – Abnormal liver function tests have been observed occasionally during Lopid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lopid is discontinued. Therefore periodic liver function studies are recommended and Lopid therapy should be terminated if abnormalities persist.

9. **Use in Children** – Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2% (23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

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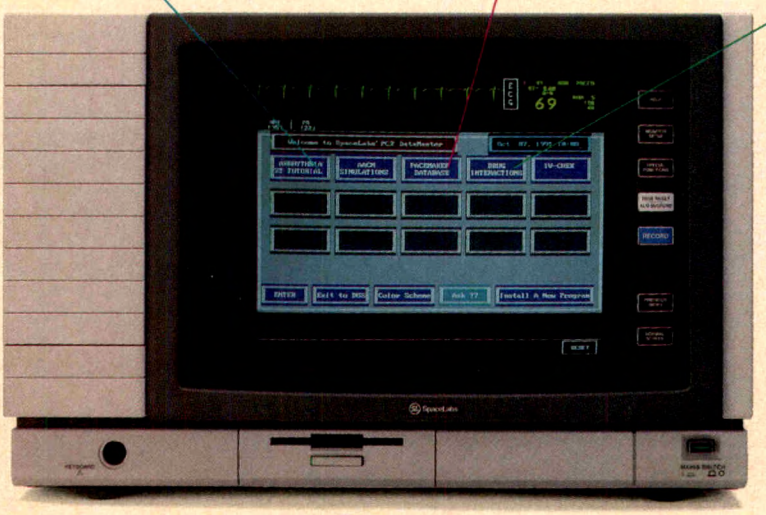
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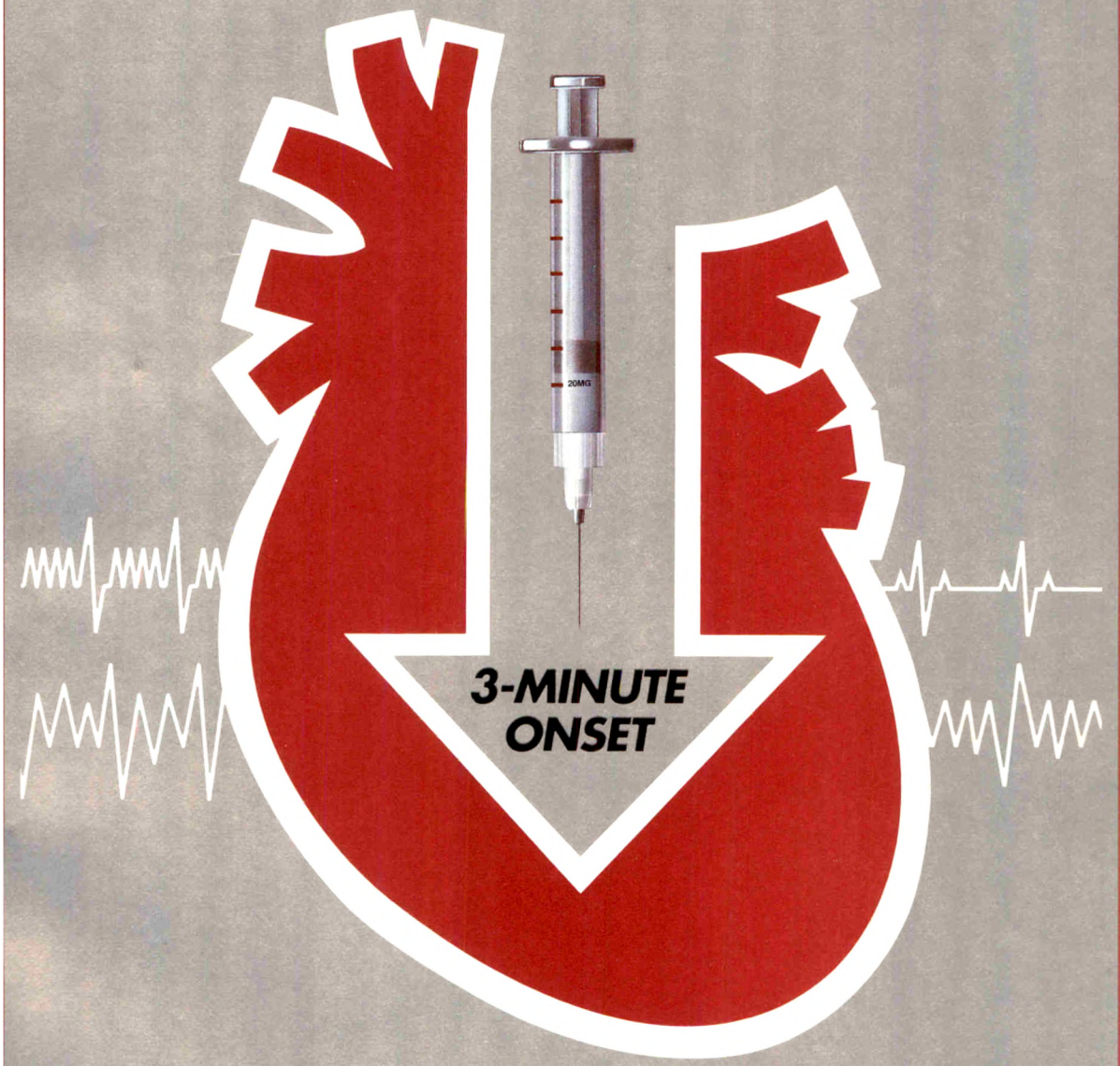
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Now for heart rate control during atrial fibrillation and flutter

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION



GAINS HEART RATE CONTROL QUICKLY...

Please see brief summary of prescribing information on last page of this advertisement.
Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

IVAG800/A6120

0154B2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION



Should be used with continuous monitoring of ECG and blood pressure to avoid hypotension or bradycardia. Infusion rate/dose should be regulated accordingly. A defibrillator and emergency equipment should be readily available.

CIVAG800/A6120

For heart rate control during atrial fibrillation and flutter

MAINTAINS HEART RATE CONTROL SAFELY

FAST

- 3-minute onset of action following bolus injection[1]
- 95% response rate within 2 to 7 minutes of administration[1]
- 1- to 3-hour duration of action with initial bolus

SAFE

- 4.3% incidence of asymptomatic hypotension[1]*
- 3.2% incidence of symptomatic hypotension[1]*
- 3.9% incidence of injection site reaction[1]
- 1.7% incidence of flushing[1]*
- Little negative inotropic effect[1]†
- Do not use in patients with WPW or short PR syndrome

  Other contraindications: sick sinus syndrome or second- or third-degree AV block, except with a functioning pacemaker; severe hypotension or shock; hypersensitivity; recent IV beta-blockers; ventricular tachycardia.

CONTINUOUS CONTROL

- Heart rate control through infusion for up to 24 hours[1,2]

  Cardizem Injectable is indicated for temporary control of rapid ventricular rate during atrial fibrillation and flutter; rarely converts to normal sinus rhythm.

*Occurs most often during or immediately following bolus injection.
†Caution should be used in patients with congestive heart failure.

CARDIZEM INJECTABLE
Heart rate control that is fast, safe, and continuous

Please see brief summary of prescribing information on next page.

0154B2

CARDIZEM® Injectable
(diltiazem hydrochloride)
BOLUS INFUSION

CONVENIENT DOSAGE

1	2	3
Beginning treatment as	If response is inadequate, wait 15 minutes	Treatment as
BOLUS: 0.25 mg/kg actual body weight over 2 minutes	**BOLUS:** 0.35 mg/kg actual body weight over 2 minutes	**INFUSION: 10* to 15 mg/hr** *5 mg/hr may be appropriate starting infusion for some patients.
20 mg average patient	**25 mg average patient**	

BRIEF SUMMARY

CARDIZEM® Injectable
(diltiazem hydrochloride)

INDICATIONS AND USAGE

CARDIZEM Injectable (diltiazem hydrochloride) is indicated for the following:

1. **Atrial Fibrillation or Atrial Flutter.** Temporary control of rapid ventricular rate in atrial fibrillation or atrial flutter. It should not be used in patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in Wolff-Parkinson-White (WPW) syndrome or short PR syndrome.
2. **Paroxysmal Supraventricular Tachycardia.** Rapid conversion of paroxysmal supraventricular tachycardias (PSVT) to sinus rhythm. This includes AV nodal reentrant tachycardias and reciprocating tachycardias associated with an extranodal accessory pathway such as the WPW syndrome or short PR syndrome. Unless otherwise contraindicated, appropriate vagal maneuvers should be attempted prior to administration of CARDIZEM Injectable.

The use of CARDIZEM Injectable for control of ventricular response in patients with atrial fibrillation or atrial flutter or conversion to sinus rhythm in patients with PSVT should be undertaken with caution when the patient is compromised hemodynamically or is taking other drugs that decrease any or all of the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium.

For either indication and particularly when employing continuous intravenous infusion, the setting should include continuous monitoring of the ECG and frequent measurement of blood pressure. A defibrillator and emergency equipment should be readily available.

In domestic controlled trials in patients with atrial fibrillation or atrial flutter, bolus administration of CARDIZEM Injectable was effective in reducing heart rate by at least 20% in 95% of patients. CARDIZEM Injectable rarely converts atrial fibrillation or atrial flutter to normal sinus rhythm. Following administration of one or two intravenous bolus doses of CARDIZEM Injectable, response usually occurs within 3 minutes and maximal heart rate reduction generally occurs in 2 to 7 minutes. Heart rate reduction may last from 1 to 3 hours. If hypotension occurs, it is generally short-lived, but may last from 1 to 3 hours.

A 24-hour continuous infusion of CARDIZEM Injectable in the treatment of atrial fibrillation or atrial flutter maintained at least a 20% heart rate reduction during the infusion in 83% of patients. Upon discontinuation of infusion, heart rate reduction may last from 0.5 hours to more than 10 hours (median duration 7 hours). Hypotension, if it occurs, may be similarly persistent.

In the controlled clinical trials, 3.2% of patients required some form of intervention (typically, use of intravenous fluids or the Trendelenburg position) for blood pressure support following CARDIZEM Injectable.

In domestic controlled trials, bolus administration of CARDIZEM Injectable was effective in converting PSVT to normal sinus rhythm in 88% of patients within 3 minutes of the first or second bolus dose.

Symptoms associated with the arrhythmia were improved in conjunction with decreased heart rate or conversion to normal sinus rhythm following administration of CARDIZEM Injectable.

CONTRAINDICATIONS

CARDIZEM Injectable is contraindicated in:

1. Patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
2. Patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker.
3. Patients with severe hypotension or cardiogenic shock.
4. Patients who have demonstrated hypersensitivity to the drug.
5. Intravenous diltiazem and intravenous beta-blockers should not be administered together or in close proximity (within a few hours).
6. Patients with atrial fibrillation or atrial flutter associated with an accessory bypass tract such as in WPW syndrome or short PR syndrome.

   As with other agents which slow AV nodal conduction and do not prolong the refractoriness of the accessory pathway (eg, verapamil, digoxin), in rare instances patients in atrial fibrillation or atrial flutter associated with an accessory bypass tract may experience a potentially life-threatening increase in heart rate accompanied by hypotension when treated with CARDIZEM Injectable. As such, the initial use of CARDIZEM Injectable should be, if possible, in a setting where monitoring and resuscitation capabilities, including DC cardioversion/defibrillation, are present (see OVERDOSAGE). Once familiarity of the patient's response is established, use in an office setting may be acceptable.
7. Patients with ventricular tachycardia. Administration of other calcium channel blockers to patients with wide complex tachycardia (QRS ≥ 0.12 seconds) has resulted in hemodynamic deterioration and ventricular fibrillation. It is important that an accurate pretreatment diagnosis distinguish wide complex QRS tachycardia of supraventricular origin from that of ventricular origin prior to administration of CARDIZEM Injectable.

WARNINGS

1. **Cardiac Conduction.** Diltiazem prolongs AV nodal conduction and refractoriness that may rarely result in second- or third-degree AV block in sinus rhythm. Concomitant use of diltiazem with agents known to affect cardiac conduction may result in additive effects (see Drug Interactions). If high-degree AV block occurs in sinus rhythm, intravenous diltiazem should be discontinued and appropriate supportive measures instituted (see OVERDOSAGE).
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function and in patients with a compromised myocardium, such as severe CHF, acute MI, and hypertrophic cardiomyopathy, have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Administration of oral diltiazem in patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission is contraindicated. Experience with the use of CARDIZEM Injectable in patients with impaired ventricular function is limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM Injectable therapy may occasionally result in symptomatic hypotension (3.2%). The use of intravenous diltiazem for control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically. In addition, caution should be used in patients taking other drugs that decrease peripheral resistance, intravascular volume, myocardial contractility or conduction.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted following oral diltiazem. Therefore, the potential for acute hepatic injury exists following administration of intravenous diltiazem.
5. **Ventricular Premature Beats (VPBs).** VPBs may be present on conversion of PSVT to sinus rhythm with CARDIZEM Injectable. These VPBs are transient, are typically considered to be benign, and appear to have no clinical significance. Similar ventricular complexes have been noted during cardioversion, other pharmacologic therapy, and during spontaneous conversion of PSVT to sinus rhythm.

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. The drug should be used with caution in patients with impaired renal or hepatic function (see WARNINGS). High intravenous dosages (4.5 mg/kg tid) administered to dogs resulted in significant bradycardia and alterations in AV conduction. In subacute and chronic dog and rat studies designed to produce toxicity, high oral doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver, which were reversible when the drug was discontinued. In dogs, oral doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatologic events progressing to erythema multiforme and/or exfoliative dermatitis have been infrequently reported following oral diltiazem. Therefore, the potential for these dermatologic reactions exists following exposure to intravenous diltiazem. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions. Due to potential for additive effects, caution is warranted in patients receiving CARDIZEM Injectable concomitantly with any agent(s) known to affect cardiac contractility and/or SA or AV node conduction (see WARNINGS).

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM (diltiazem hydrochloride) undergoes extensive metabolism by the cytochrome P-450 mixed function oxidase system. Although specific pharmacokinetic drug-drug interaction studies have not been conducted with single intravenous injection or constant rate intravenous infusion, coadministration of CARDIZEM Injectable with other agents which primarily undergo the same route of biotransformation may result in competitive inhibition of metabolism.

Digitalis: Intravenous diltiazem has been administered to patients receiving either intravenous or oral digitalis therapy. The combination of the two drugs was well tolerated without serious adverse effects. However, since both drugs affect AV nodal conduction, patients should be monitored for excessive slowing of the heart rate and/or AV block.

Beta-blockers: Intravenous diltiazem has been administered to patients on chronic oral beta-blocker therapy. The combination of the two drugs was generally well tolerated without serious adverse effects. If intravenous diltiazem is administered to patients receiving chronic oral beta-blocker therapy, the possibility for bradycardia, AV block, and/or depression of contractility should be considered (see CONTRAINDICATIONS). ***Oral*** administration of diltiazem with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. In vitro, propranolol appears to be displaced from its binding sites by diltiazem.

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats at oral dosage levels of up to 100 mg/kg/day, and a 21-month study in mice at oral dosage levels of up to 30 mg/kg/day showed no evidence of carcinogenicity. There was also no mutagenic response in vitro or in vivo in mammalian cell assays or in vitro in bacteria. No evidence of impaired fertility was observed in a study performed in male and female rats at oral dosages of up to 100 mg/kg/day.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of oral doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended oral antianginal therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human oral antianginal dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report with oral diltiazem suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The following adverse reaction rates are based on the use of CARDIZEM Injectable in over 400 domestic clinical trial patients with atrial fibrillation/flutter or PSVT under double-blind or open-label conditions. Worldwide experience in over 1,300 patients was similar.

Adverse events reported in controlled and uncontrolled clinical trials were generally mild and transient. Hypotension was the most commonly reported adverse event during clinical trials. Asymptomatic hypotension occurred in 4.3% of patients. Symptomatic hypotension occurred in 3.2% of patients. When treatment for hypotension was required, it generally consisted of administration of saline or placing the patient in the Trendelenburg position. Other events reported in at least 1% of the diltiazem-treated patients were injection site reactions (eg, itching, burning)—3.9%, vasodilation (flushing)—1.7%, and arrhythmia (junctional rhythm or isorhythmic dissociation)—1.0%.

In addition, the following events were reported infrequently (less than 1%):

Cardiovascular:	Atrial flutter, AV block first degree, AV block second degree, bradycardia, chest pain, congestive heart failure, sinus pause, sinus node dysfunction, syncope, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia.
Dermatologic:	Pruritus, sweating.
Gastrointestinal:	Constipation, elevated SGOT or alkaline phosphatase, nausea, vomiting.
Nervous System:	Dizziness, paresthesia.
Other:	Amblyopia, asthenia, dry mouth, dyspnea, edema, headache, hyperuricemia.

Although not observed in clinical trials with CARDIZEM Injectable, other reactions associated with oral diltiazem may occur.

Product information as of October 1991

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The American Journal of Cardiology®

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CORONARY ARTERY DISEASE

1251

Predictive Value of Apolipoproteins in a Prospective Survey of Coronary Artery Disease in Men

Gunnar Sigurdsson, Asdis Baldursdottir, Helgi Sigvaldason, Uggi Agnarsson, Gudmundur Thorgeirsson, and Nikulas Sigfusson

The independent prognostic value of apolipoproteins (apo-B, apo-AI and apo[a]) with regard to coronary artery disease was estimated from a prospective survey among 1,332 randomly selected Icelandic men, aged 45 to 72 years, participating in a health survey from 1979 to 1981. The group was followed for 8.6 years, and during that period 104 men had fatal or nonfatal myocardial infarction. The Cox's proportional hazards model was used to estimate the significance of independent variables. The results of multivariate analysis showed that apo(a) was a significant independent risk factor (odds ratio 1.22 for 1 SD), but apo-AI was a stronger negative risk factor (odds ratio 0.70 for 1 SD). Apo-B was a highly significant risk factor in a univariate analysis, but not in a multivariate analysis when serum cholesterol was included. The results illustrate additional importance of apo-AI and apo(a) concentrations in predicting coronary artery disease, whereas apo-B did not contribute anything further to the prediction than serum cholesterol.

1255

Increased IgM-Anticardiolipin Antibodies in Patients with Restenosis After Percutaneous Transluminal Coronary Angioplasty

Bernd Eber, Martin Schumacher, Piet Auer-Grumbach, Hermann Toplak, and Werner Klein

IgM- and IgG-anticardiolipin antibodies (acL) were determined in 65 men with coronary artery disease treated by percutaneous transluminal coronary angioplasty (PTCA). Follow-up angiography was performed 12 months after PTCA. The series was divided in 2 groups: 34 with (≥50% reduction in vessel diameter) and 31 without restenosis. Medical history and laboratory findings were comparable in both groups. In patients with restenosis, IgM-acL, but not IgG-acL, were significantly increased compared with those in patients without restenosis. No correlation could be found between known risk factors and acL levels. Thus, IgM-acL appear to be independent markers indicating a risk for restenosis after PTCA.

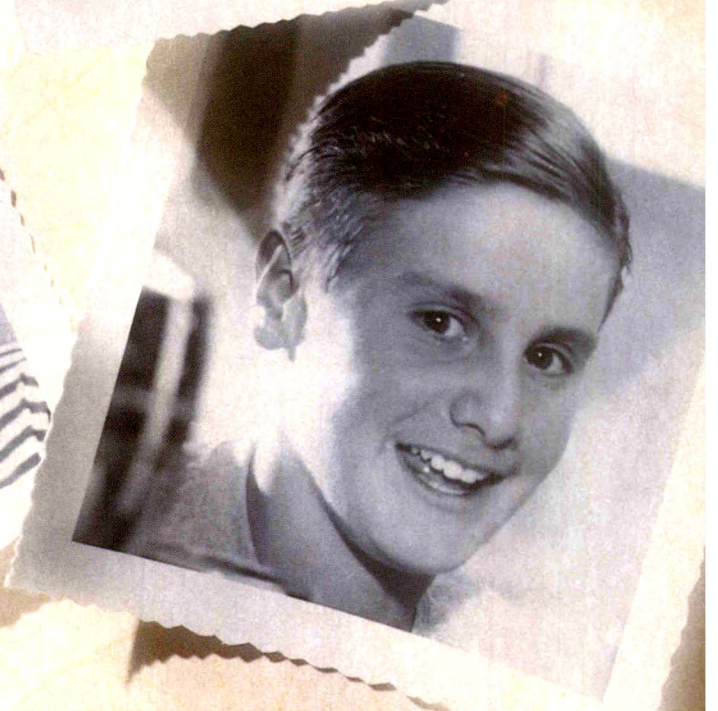
Continued on page A17

THEY WERE CAREFREE...

They were raised in a simpler time, before sugar-free and fat-free. Now hypertension, often with elevated cholesterol and blood sugar, enters the picture...







NOW THEY'RE CONCERNED...

Today's hypertensives with new concerns...

THE CARDURA



*Adapted from the interim (12 months) results of the Treatment of Mild Hypertension Study, a randomized, double-blind, placebo-controlled trial of a nutritional-hygienic regimen along with various drug therapies. All drugs (except acebutolol) were given initially in low doses. If the patient showed a diastolic blood pressure more than 95 mm Hg on three successive follow-up visits, the dosage was doubled. If blood pressure remained elevated, a second drug (chlorthalidone, except for chlorthalidone group, which was given enalapril) was added. Mean diastolic blood pressure was lowered in the various drug groups with median dosages, as follows: doxazosin (2 mg/day), 12.0 mm Hg; enalapril (5 mg/day), 12.2 mm Hg; chlorthalidone (15 mg/day), 13.1 mm Hg; and acebutolol (400 mg/day), 13.7 mm Hg (n=847; $P<0.01$ vs placebo).

†n=128; $P<0.01$ vs placebo. In a pooled analysis of placebo-controlled studies with about 300 predominantly normocholesterolemic patients per treatment group, CARDURA produced a small decrease in total cholesterol (-2.7%) and LDL cholesterol (-4.3%) and a small increase in the HDL/total cholesterol ratio (+4.3%).

‡Adapted from Lehtonen et al[2] (n=77; after 26 weeks: $P<0.001$ compared with week 0 for blood pressure and insulin, $P<0.05$ compared with week 0 for glucose).

GENERATION



Choose CARDURA: first-line therapy for a new generation of hypertensives.

Choose CARDURA for blood pressure control that doesn't jeopardize blood lipids.

In the Treatment of Mild Hypertension Study, CARDURA lowered diastolic blood pressure (mean 12.0 mm Hg) as effectively as enalapril, chlorthalidone, and acebutolol[1*]

CARDURA lowered blood pressure with a small increase in the HDL/total cholesterol ratio (+2.4%)* in the same study.[1†] The clinical significance of these changes is uncertain. Cholesterol is just one parameter to consider when selecting the best individualized therapy for a given patient

Choose CARDURA for blood pressure control that doesn't compromise blood sugar.

CARDURA controlled diastolic blood pressure without an adverse effect on glucose tolerance or insulin control[2‡]

CARDURA is well tolerated. In placebo-controlled studies, only three common side effects were reported significantly more often than placebo: dizziness, somnolence, and fatigue.[§]

Only 2% of patients discontinued therapy due to adverse effects—the same as with placebo

§ These were generally mild and transient. Syncope has been reported, but rarely (<1%).

ONCE-A-DAY

CARDURA®

(doxazosin mesylate) Scored Tablets 1 mg, 2 mg, 4 mg, 8 mg

HYPERTENSION CONTROL FOR A NEW GENERATION.

Please see brief summary on last page.

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CARDURA® (doxazosin mesylate) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

CARDURA (doxazosin mesylate) is indicated for the treatment of hypertension. CARDURA may be used alone or in combination with diuretics or beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with angiotensin converting enzyme inhibitors or calcium channel blockers.

CONTRAINDICATIONS

CARDURA is contraindicated in patients with a known sensitivity to quinazolines (e.g. prazosin, terazosin).

WARNINGS

Syncope and "First-dose" Effect:

Doxazosin, like other alpha-adrenergic blocking agents, can cause marked hypotension, especially in the upright position, with syncope and other postural symptoms such as dizziness. Marked orthostatic effects are most common with the first dose but can also occur when there is a dosage increase, or if therapy is interrupted for more than a few days. To decrease the likelihood of excessive hypotension and syncope, it is essential that treatment be initiated with the 1 mg dose. The 2, 4, and 8 mg tablets are not for initial therapy. Dosage should then be adjusted slowly (see DOSAGE AND ADMINISTRATION section) with increases in dose every two weeks. Additional antihypertensive agents should be added with caution.

Patients being titrated with doxazosin should be cautioned to avoid situations where injury could result should syncope occur.

In an early investigational study of the safety and tolerance of increasing daily doses of doxazosin in normotensives beginning at 1 mg/day, only 2 of 6 subjects could tolerate more than 2 mg/day without experiencing symptomatic postural hypotension. In another study of 24 healthy normotensive male subjects receiving initial doses of 2 mg/day of doxazosin, seven (29%) of the subjects experienced symptomatic postural hypotension between 0.5 and 6 hours after the first dose necessitating termination of the study. In this study 2 of the normotensive subjects experienced syncope. Subsequent trials in hypertensive patients always began doxazosin dosing at 1 mg/day resulting in a 4% incidence of postural side effects at 1 mg/day with no cases of syncope.

In multiple dose clinical trials involving over 1500 patients with dose titration every one to two weeks, syncope was reported in 0.7% of patients. None of these events occurred at the starting dose of 1 mg and 1.2% (8/664) occurred at 16 mg/day.

If syncope occurs, the patient should be placed in a recumbent position and treated supportively as necessary.

PRECAUTIONS

General

1. Orthostatic Hypotension:

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure, such as dizziness, lightheadedness, or vertigo, can occur, especially at initiation of therapy or at the time of dose increases. These were common in clinical trials, occurring in up to 23% of all patients treated and causing discontinuation of therapy in about 2%.

In placebo controlled titration trials orthostatic effects were minimized by beginning therapy at 1 mg per day and titrating every two weeks to 2, 4, or 8 mg per day. There was an increased frequency of orthostatic effects in patients given 8 mg or more, 10%, compared to 5% at 1-4 mg and 3% in the placebo group.

Patients in occupations in which orthostatic hypotension could be dangerous should be treated with particular caution.

If hypotension occurs, the patient should be placed in the supine position and, if this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

2. Impaired liver function:

CARDURA should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism (see CLINICAL PHARMACOLOGY). There is no controlled clinical experience with CARDURA in patients with these conditions.

3. Leukopenia/Neutropenia:

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean WBC (N=474) and mean neutrophil counts (N=419) were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs. A search through a data base of 2400 patients revealed 4 in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm³ range over periods of 20 and 40 weeks. In cases where follow-up was available the WBCs and neutrophil counts returned to normal after discontinuation of CARDURA. No patients became symptomatic as a result of the low WBC or neutrophil counts.

Information for Patients:

Patients should be made aware of the possibility of syncopal and orthostatic symptoms, especially at the initiation of therapy, and urged to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur during initiation of doxazosin therapy. They should also be advised of the need to sit or lie down when symptoms of lowered blood pressure occur, although these symptoms are not always orthostatic, and to be careful when rising from a sitting or lying position. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician, so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with doxazosin, requiring caution in people who must drive or operate heavy machinery.

Drug Interactions:

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that CARDURA has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. There is no information on the effect of other highly plasma protein bound drugs on doxazosin binding. CARDURA has been administered without any evidence of an adverse drug interaction to patients receiving thiazide diuretics, beta blocking agents, and nonsteroidal anti-inflammatory drugs.

Drug/Laboratory test interactions:

None known.

Cardiac Toxicity in Animals:

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day (150 times the maximum recommended human dose assuming a patient weight of 60 kg). Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (up to 10 or 20 mg/kg/day, depending on the study) in either species. These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 mg/kg/day and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Chronic dietary administration (up to 24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg: about 150 times the maximum recommended human dose of 16 mg/60 kg) revealed no evidence of carcinogenicity in rats. There was also no evidence of carcinogenicity in a similarly conducted study (up to 18 months of dietary administration) in mice. The mouse study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin.

Mutagenicity studies revealed no drug- or metabolite-related effects at either chromosomal or subchromosomal levels.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 75 times the maximum recommended human dose. This effect was reversible within two weeks of drug withdrawal.

Pregnancy

Teratogenic Effects, Pregnancy Category B. Studies in rabbits and rats at daily oral doses of up to 40 and 20 mg/kg, respectively (150 and 75 times the maximum recommended daily dose of 16 mg, assuming a patient weight of 60 kg), have revealed no evidence of harm to the fetus. The rabbit study, however, was compromised by the failure to use a maximally tolerated dose of doxazosin. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA should be used during pregnancy only if clearly needed.

Radioactivity was found to cross the placenta following oral administration of labelled doxazosin to pregnant rats.

Nonteratogenic Effects. In peri-postnatal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.



Nursing Mothers

Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum concentration about 20 times greater than the maternal plasma concentration. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when CARDURA is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

CARDURA has been administered to approximately 4000 patients, of whom 1679 were included in the clinical development program. In that program, minor adverse effects were frequent, but led to discontinuation of treatment in only 7% of patients. In placebo-controlled studies adverse effects occurred in 49% and 40% of patients in the doxazosin and placebo groups, respectively, and led to discontinuation in 2% of patients in each group. The major reasons for discontinuation were postural effects (2%), edema, malaise/fatigue, and some heart rate disturbance, each about 0.7%.

In controlled clinical trials directly comparing CARDURA to placebo there was no significant difference in the incidence of side effects, except for dizziness (including postural), weight gain, somnolence and fatigue/malaise. Postural effects and edema appeared to be dose related.

The prevalence rates presented below are based on combined data from placebo-controlled studies involving once daily administration of doxazosin at doses ranging from 1-16 mg. Table 1 summarizes those adverse experiences (possibly/probably related) reported for patients in these studies where the prevalence rate in the doxazosin group was at least 0.5% or where the reaction is of particular interest.

TABLE 1
ADVERSE REACTIONS DURING PLACEBO CONTROLLED STUDIES

		DOXAZOSIN (N=339)	PLACEBO (N=336)
CARDIOVASCULAR:	Dizziness	19%	9%
	Vertigo	2%	1%
	Postural Hypotension	0.3%	0%
	Edema	4%	3%
	Palpitation	2%	3%
	Arrhythmia	1%	0%
	Hypotension	1%	0%
	Tachycardia	0.3%	1%
	Peripheral Ischemia	0.3%	0%
SKIN APPENDAGES:	Rash	1%	1%
	Pruritus	1%	1%
MUSCULOSKELETAL:	Arthralgia/Arthritis	1%	0%
	Muscle Weakness	1%	0%
	Myalgia	1%	0%
CENTRAL & PERIPHERAL N.S.:	Headache	14%	16%
	Paresthesia	1%	1%
	Kinetic Disorders	1%	0%
	Ataxia	1%	0%
	Hypertonia	1%	0%
	Muscle Cramps	1%	0%
AUTONOMIC:	Mouth Dry	2%	2%
	Flushing	1%	0%
SPECIAL SENSES:	Vision Abnormal	2%	1%
	Conjunctivitis/Eye Pain	1%	1%
	Tinnitus	1%	0.3%
PSYCHIATRIC:	Somnolence	5%	1%
	Nervousness	2%	2%
	Depression	1%	1%
	Insomnia	1%	1%
	Sexual Dysfunction	2%	1%
GASTROINTESTINAL:	Nausea	3%	4%
	Diarrhea	2%	3%
	Constipation	1%	1%
	Dyspepsia	1%	1%
	Flatulence	1%	1%
	Abdominal Pain	0%	2%
	Vomiting	0%	1%
RESPIRATORY:	Rhinitis	3%	1%
	Dyspnea	1%	1%
	Epistaxis	1%	0%
URINARY:	Polyuria	2%	0%
	Urinary Incontinence	1%	0%
	Micturation Frequency	0%	2%
GENERAL:	Fatigue/Malaise	12%	6%
	Chest Pain	2%	2%
	Asthenia	1%	1%
	Face Edema	1%	0%
	Pain	2%	2%

Additional adverse reactions have been reported, but these are, in general, not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin. The following adverse reactions occurred with a frequency of between 0.5% and 1%: syncope, hypoesthesia, increased sweating, agitation, increased weight. The following additional adverse reactions were reported by <0.5% of 3960 patients who received doxazosin in controlled or open, short- or long-term clinical studies, including international studies. *Cardiovascular System:* angina pectoris, myocardial infarction, cerebrovascular accident; *Autonomic Nervous System:* pallor; *Metabolic:* thirst, gout, hypokalemia; *Hematopoietic:* lymphadenopathy, purpura; *Reproductive System:* breast pain; *Skin Disorders:* alopecia, dry skin, eczema; *Central Nervous System:* paresis, tremor, twitching, confusion, migraine, impaired concentration; *Psychiatric:* paroniria, amnesia, emotional lability, abnormal thinking, depersonalization; *Special Senses:* parosmia, earache, taste perversion, photophobia, abnormal lacrimation; *Gastrointestinal System:* increased appetite, anorexia, fecal incontinence, gastroenteritis; *Respiratory System:* bronchospasm, sinusitis, coughing, pharyngitis; *Urinary System:* renal calculus; *General Body System:* hot flushes, back pain, infection, fever/rigors, decreased weight, influenza-like symptoms.

CARDURA has not been associated with any clinically significant changes in routine biochemical tests. No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen, creatinine or liver function tests. CARDURA has been associated with decreases in white blood cell counts (See Precautions).

OVERDOSAGE

The oral LD_{50} of doxazosin is greater than 1000 mg/kg in mice and rats. The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The initial dosage of CARDURA in hypertensive patients is 1 mg given once daily. This starting dose is intended to minimize the frequency of postural hypotension and first dose syncope associated with CARDURA. Postural effects are most likely to occur between 2 and 6 hours after a dose. Therefore blood pressure measurements should be taken during this time period after the first dose and with each increase in dose. Depending on the individual patient's standing blood pressure response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg and 16 mg to achieve the desired reduction in blood pressure. **Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo, postural hypotension. At a titrated dose of 16 mg once daily the frequency of postural effects is about 12% compared to 3% for placebo.**

HOW SUPPLIED

CARDURA (doxazosin mesylate) is available as colored tablets for oral administration. Each tablet contains doxazosin mesylate equivalent to 1 mg (white), 2 mg (yellow), 4 mg (orange) or 8 mg (green) of the active constituent, doxazosin.

CARDURA® TABLETS are available as 1 mg (white), 2 mg (yellow), 4 mg (orange) and 8 mg (green) scored tablets.

Bottles of 100: 1 mg (NDC 0049-2750-66), 2 mg (NDC 0049-2760-66), 4 mg (NDC 0049-2770-66), 8 mg (NDC 0049-2780-66)

Recommended Storage: Store below 86°F(30°C).

CAUTION: Federal law prohibits dispensing without prescription.

65-4538-00-0 Issued Nov 1990

References: 1. The Treatment of Mild Hypertension Research Group. The Treatment of Mild Hypertension Study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **2.** Lehtonen A, the Finnish Multicenter Study Group. Lowered levels of serum insulin, glucose, and cholesterol in hypertensive patients during treatment with doxazosin. *Curr Ther Res.* 1990;47:278-284.

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1259
Safety and Clinical Use of Exercise Testing One to Three Days After Percutaneous Transluminal Coronary Angioplasty
Gary J. Balady, Mark L. Leitschuh, Alice K. Jacobs, Denise Merrell, Donald A. Weiner, and Thomas J. Ryan

To evaluate both the safety and clinical use of predischarge symptom-limited exercise testing after successful uncomplicated percutaneous transluminal coronary angioplasty (PTCA), 100 patients were randomized to undergo exercise testing (n = 50) or no exercise testing (n = 50). Patients who exercise achieved 71 ± 12% of predicted maximal heart rate, with 38% reaching ≥ stage III of the Bruce protocol without complications. Of 11 patients with a positive test response, 92% had angiographically incomplete revascularization. Questionnaires administered to attending physicians both before and after testing demonstrated that patients in the exercise group (with a negative test) were allowed to perform various activities earlier after PTCA compared with those in the no-exercise group. Thus, symptom-limited exercise testing after PTCA appears to be safe, and may be useful in patient management at the time of hospital discharge.

1265
Transthoracic High-Frequency Two-Dimensional Echocardiography, Doppler and Color Flow Mapping to Determine Anatomy and Blood Flow Patterns in the Distal Left Anterior Descending Coronary Artery
Antoinette Kenny and Leonard M. Shapiro

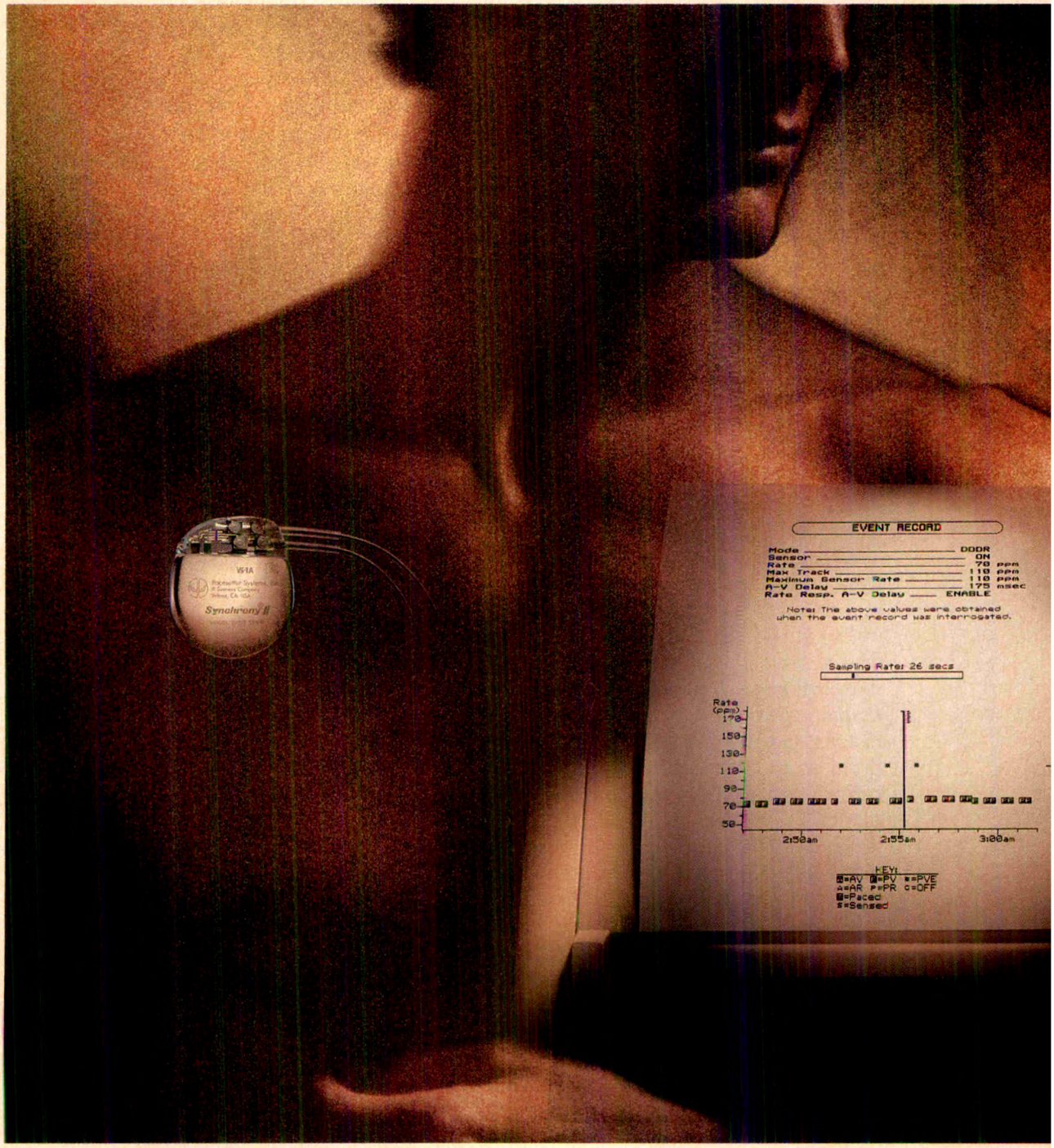
The distal left anterior descending coronary artery was successfully imaged, and characteristic biphasic flow was detected using transthoracic high-frequency ultrasound and Doppler in 19 of 56 consecutive patients (34%) studied. The distal left anterior descending coronary artery appeared normal by ultrasound in 18 patients, and a significant stenosis was detected in 1; angiography confirmed the ultrasound findings. Color flow mapping demonstrated normal laminar flow, except in the patient with a distal stenosis. Pulsed Doppler confirmed an increased diastolic velocity distal to the stenosis. This is the first transthoracic evaluation of the hemodynamic effects of a coronary stenosis, and the first in vivo description of blood flow disturbance at a distal coronary stenosis in humans. Although the clinical use of this technique is limited, it may have important implications in the noninvasive assessment of coronary artery dimensions and relative changes in blood flow.

1269
Accuracy of Dobutamine Stress Echocardiography in Detecting Coronary Artery Disease
Pamela A. Marcovitz and William F. Armstrong

Dobutamine stress echocardiography (DSE) was performed in 141 patients undergoing coronary arteriography. For all patients, DSE had a sensitivity of 96%, specificity of 66% and overall accuracy of 89%. For patients with normal resting wall motion, DSE had a sensitivity of 87%, specificity of 91% and accuracy of 89%. Sensitivity and specificity were similar in anterior and posterior coronary territories, and in patients re-

Continued on page A20

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ceiving antianginal therapy. Dobutamine was well-tolerated by most patients, and no serious complications were observed. DSE is a clinically feasible and accurate means for detecting coronary artery disease.

1274

Comparison of the Clinical Profile and Outcome of Women and Men in Cardiac Rehabilitation

Lauralyn B. Cannistra, Gary J. Balady, Carol J. O'Malley, Donald A. Weiner, and Thomas J. Ryan

A comparison was made between the clinical profile and outcome of 51 women and 174 men consecutively enrolled in an urban, multidisciplinary, exercise-based cardiac rehabilitation program. Compared with men, more women were nonwhite, unemployed, unmarried, hypertensive or diabetic, and had higher cholesterol ($p < 0.01$). Compliance rates were similar for women (51%) and men (63%) (p = not significant). Univariate predictors of program noncompliance differed between women and men. After training, women increased their exercise time by 31% and peak METs by 30% ($p < 0.001$). Men demonstrated a similar training effect, with a 21% increase in exercise time and a 16% increase in peak METs ($p < 0.001$). Thus, in this cardiac rehabilitation program, women have a less favorable risk factor profile and differ from men with regard to baseline demographics and predictors of program completion. Women, however, have similar rates of compliance and can achieve the same improvement in functional capacity with training.

1280

Usefulness of Dipyridamole-Thallium Scanning for Preoperative Evaluation of Cardiac Risk for Nonvascular Surgery

Christopher M. Coley, Terry S. Field, Stephen A. Abraham, Charles A. Boucher, and Kim A. Eagle

One hundred consecutive patients with known or suspected coronary artery disease who underwent nonvascular surgery were studied to determine the usefulness of clinical markers and planar dipyridamole-thallium scanning (DTS) in stratifying perioperative cardiac risk. Nine patients (9%) had ≥ 1 serious cardiac event. Multivariate analysis revealed that age >70 years, history of heart failure, and thallium redistribution with DTS were independent predictors of risk. There were no cardiac events in the 45 patients without the 2 clinical variables. For patients with 1 or both clinical markers, thallium redistribution correlates with substantial change in perioperative cardiac risk. It is concluded that preoperative DTS is most useful in assessing risk in selected nonvascular surgery patients at intermediate or high risk by clinical descriptors. For almost half the patients with known or suspected coronary artery disease, DTS may be unnecessary.

Continued on page A24


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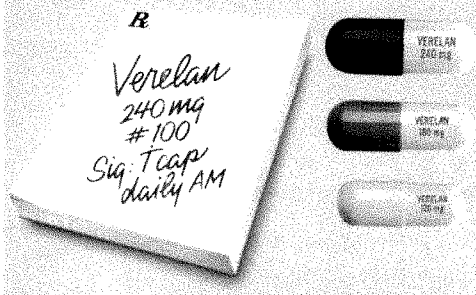
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VERELAN®

Verapamil HCl 120 mg 180 mg 240 mg

PELLET-FILLED CAPSULES



ENGINEERED FOR THE CONTROL YOU WANT, THE PROTECTION THEY NEED.

The usual dose is 240 mg once daily. If adequate response is not obtained, the dose may be titrated up to 360 mg or 480 mg once daily. VERELAN 120 mg is available for patients requiring lower-dose verapamil therapy.

And now...

THE VERELAN PLEDGE

Following appropriate dose titration, VERELAN will control blood pressure at the 24th hour after dosing, or your patients will be reimbursed 100% of their out-of-pocket costs for their most recent VERELAN prescription. See your VERELAN representative for more details.

References: 1. Carr AA, Bottini PB, Prisant LM, et al. Once-daily verapamil in the treatment of mild-to-moderate hypertension: a double-blind placebo-controlled dose-ranging study. *J Clin Pharmacol.* 1991;31:144-150. 2. Data on file for VERELAN 240 mg, Lederle Laboratories, Pearl River, NY.

Brief Summary

VERELAN®
Verapamil HCl
Sustained-Release Pellet-Filled Capsules

For complete Prescribing Information, consult package insert.

CLINICAL PHARMACOLOGY

Food does not affect the extent or rate of the absorption of verapamil from the controlled release VERELAN capsule.

Atrioventricular block can occur in patients without preexisting condition defects (see **WARNINGS**).

Acceleration of ventricular rate and/or ventricular fibrillation has been reported in patients with atrial flutter or atrial fibrillation and a coexisting accessory AV pathway following administration of verapamil (see **WARNINGS**).

In patients with hepatic insufficiency, metabolism is delayed and elimination half-life prolonged up to 14 to 16 hours (see **PRECAUTIONS**), the volume of distribution is increased, and plasma clearance reduced to about 30% of normal.

CONTRAINDICATIONS

Severe LV dysfunction (see **WARNINGS**), hypotension (systolic pressure <90 mmHg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), second- or third-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), (see **WARNINGS**), hypersensitivity to verapamil.

WARNINGS

Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction <30%) or moderate-to-severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta blocker. Control milder heart failure with optimum digitalization and/or diuretics before VERELAN is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported.

Several cases of hepatocellular injury have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving IV verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (second- or third-degree, 0.8%). Development of marked first-degree block or progression to second- or third-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, second-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

PRECAUTIONS

Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol clearance may occur with combined use. Chronic verapamil treatment can

VERELAN® verapamil HCl

increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Verapamil has been given concomitantly with short- and long-acting nitrates without any undesirable drug interactions. Interaction between cimetidine and chronically administered verapamil has not been studied. In healthy volunteers, clearance of verapamil was reduced or unchanged. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully.

Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporine. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. **Pregnancy Category C**. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use. Safety and efficacy of verapamil in children below the age of 18 years have not been established.

ADVERSE REACTIONS

Reversible (upon discontinuation of verapamil) nonobstructive, paralytic ileus has been infrequently reported in association with the use of verapamil.

In clinical trials with 285 hypertensive patients on VERELAN for more than 1 week, the following adverse reactions were reported: constipation (7.4%); headache (5.3%); dizziness (4.2%); lethargy (3.2%); dyspepsia (2.5%); rash (1.4%); ankle edema (1.4%); sleep disturbance (1.4%); myalgia (1.1%). In clinical trials of other formulations of verapamil HCl (N = 4,954), the following reactions have occurred at rates greater than 1.0%: constipation (7.3%); dizziness (3.3%); nausea (2.7%); hypotension (2.5%); edema (1.9%); headache (2.2%); rash (1.2%); CHF/pulmonary edema (1.8%); fatigue (1.7%); bradycardia (HR<50/min) (1.4%); AV block-total 1°, 2°, 3° (1.2%); 2° and 3° (0.8%); flushing (0.6%); elevated liver enzymes (see **WARNINGS**).

The following reactions, reported in 1.0% or less of patients, occurred under conditions (open trials, marketing experience) where a causal relationship is uncertain. **Cardiovascular:** angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope. **Digestive System:** diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia. **Hemic and Lymphatic:** ecchymosis or bruising. **Nervous System:** cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence. **Respiratory:** dyspnea. **Skin:** arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculae, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme. **Special Senses:** blurred vision. **Urogenital:** gynecomastia, impotence, increased urination, spotty menstruation.

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American Cyanamid Company
Pearl River, NY 10965

by ELAN PHARMACEUTICAL RESEARCH CORP.
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Magnesium Oxide U.S.P. 140mg. Capsules
(84.5 mg. Elemental Magnesium-6.93 mEq.)

AVAILABLE THROUGH PHARMACIES ONLY

SEE THE P.D.R. FOR MORE DETAILS

SAMPLE AND LITERATURE AVAILABLE UPON REQUEST

INDICATIONS:
HYPOMAGNESEMIA, MAGNESIUM DEFICIENCIES and/or MAGNESIUM DEPLETION *resulting from diuretic and/or digitalis therapy*[1], alcoholism[2], Cisplatin[3], Amphotericin B[4], Cyclosporin[5], perenteral nutrition[6], mannitol[7], Aminoglycosides[8], and diets low in Magnesium.

Note: May aid in preventing Calcium Oxaluria

SYMPTOMS: Refractory Hypokalemia, Tremors, and cramping of extremities and tongue, grimaces, myoclonic jerks, Chvostek's sign, ataxia, irritability, disorientation, convulsion, psychotic behavior.

CAUTION: Magnesium should be used with caution in renal insufficiency. If aperient, reduce dosage.

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Erlanger, Ky. 41018
Phone: (606) 283-9437

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1286
Quantitative Angiographic and Statistical Methods to Assess Serial Changes in Coronary Luminal Diameter and Implications for Atherosclerosis Regression Trials
C. Michael Gibson, Tamas Sandor, Peter H. Stone, Richard C. Pasternak, Bernard Rosner, and Frank M. Sacks

The frame-to-frame variability in coronary diameter was evaluated, and it was determined that averaging 5 cineframes allows the detection of a 0.27 mm change in minimum diameter, and a 7.8% change in percent stenosis in individual arteries so that they can be classified as progressing or regressing. A novel statistical method that takes into account the correlation in the rate of lesion progression among multiple lesions within individual patients was applied. The correlation for the change in percent stenosis among multiple lesions in the same patient was low ($r = 0.01$), indicating that disease progression in different lesions within the same patient occurs at independent rates. With use of this statistical method and a lesion-based analysis, only 50 patients per treatment group would be needed to detect a 5.5% difference between treatment group means in the change in minimum diameter, and a 2.7% percentage point difference in the change in percent stenosis in an atherosclerosis regression study.

1291
Characterization of Acute Myocardial Infarction by Magnetic Resonance Imaging
Donald L. Johnston, Richard E. Wendt III, Sharon L. Mulvagh, and Howard Rubin

To further characterize signal-intensity changes associated with acute myocardial infarction, 17 patients had magnetic resonance imaging 6 days after presentation, using a spin-echo pulse sequence capable of suppressing motion artifact. The results indicate that infarction is often a heterogenous mixture of transmural and nontransmural injury with regions of hypointensity suggestive of intramural hemorrhage. The presence of wall thickening in many of these segments suggests that viable myocardium can be identified using this technique.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

1296
Reproducibility of Electrophysiologic Testing During Antiarrhythmic Therapy for Ventricular Arrhythmias Secondary to Coronary Artery Disease
Kevin J. Ferrick, Joshua Luce, Sara Miller, Anthony D. Mercando, Soo G. Kim, James A. Roth, and John D. Fisher

Sixty-four patients with sustained ventricular arrhythmias inducible during electrophysiologic testing underwent repeat electrophysiologic study during antiarrhythmic drug therapy that was determined to be effective as assessed by an initial drug study. Antiarrhythmic drug efficacy was confirmed in 77% of patients. Sustained ventricular tachycardia was induced at repeat electrophysiologic study in 19% of patients during antiarrhyth-

Continued on page A31

Even in mild to moderate heart failure, when diuretics and digitalis are not enough



ADDING CAPOTEN DOES MORE FOR PATIENTS SO THEY CAN DO MORE FOR THEMSELVES.*[1,2]

IN HEART FAILURE

CAPOTEN®
(captopril)
12.5 mg, 25 mg, 50 mg, 100 mg Scored Tablets

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

***CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.**

Please see brief summary, including the **boxed WARNING regarding Use in Pregnancy,** on the adjacent page.

CAPOTEN® TABLETS
Captopril Tablets

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, CAPOTEN should be discontinued as soon as possible. **See WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

WARNINGS: Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Neutropenia / Agranulocytosis: Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins >1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses >150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS: Drug Interactions.) In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension is more likely to occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

Fetal / Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. No teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension–Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. (See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS: Altered Laboratory Findings.) *Hyperkalemia:* Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Drug Interactions; ADVERSE REACTIONS: Altered Laboratory Findings.) *Cough*—Cough has been reported with the use of ACE inhibitors. Characteristically, the cough is nonproductive, persistent and resolves after discontinuation of therapy. ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Pregnancy. Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions: *Hypotension–Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Lithium—Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Nursing Mothers: Concentrations of captopril in human milk are approximately one percent of those in maternal blood. Because of the potential for serious adverse reactions in nursing infants from captopril, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of CAPOTEN to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use: Safety and effectiveness in children have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.

Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported.

CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal: About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic: Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic: Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular: Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension with captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia: Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months).

Angioedema: Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS.)

Cough: Cough has been reported in 0.5-2% of patients treated with captopril in clinical trials (see PRECAUTIONS: General: *Cough*).

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

General: Asthenia, gynecomastia.
Cardiovascular: Cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.
Dermatologic: Bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.
Gastrointestinal: Pancreatitis, glossitis, dyspepsia.
Hematologic: Anemia, including aplastic and hemolytic.
Hepatobiliary: Jaundice, hepatitis, including rare cases of necrosis, cholestasis.
Metabolic: Symptomatic hyponatremia.
Musculoskeletal: Myalgia, myasthenia.
Nervous/Psychiatric: Ataxia, confusion, depression, nervousness, somnolence.
Respiratory: Bronchospasm, eosinophilic pneumonitis, rhinitis.
Special Senses: Blurred vision.
Urogenital: Impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality
See WARNINGS: Fetal/Neonatal Morbidity and Mortality.

Altered Laboratory Findings: *Serum Electrolytes:* Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (see PRECAUTIONS).

Hyponatremia: particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine: Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of long-standing or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic: A positive ANA has been reported.

Liver Function Tests: Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure.

While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of: 12.5 mg in bottles of 100 and 1000; 25 mg in bottles of 100 and 1000; 50 mg in bottles of 100 and 1000; 100 mg of bottles of 100; and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658Z)

References: 1. The Captopril-Digoxin Multicenter Research Group: Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. *JAMA* 259:539-544, 1988. 2. Captopril Multicenter Research Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *JACC* 2:755-763, 1983.

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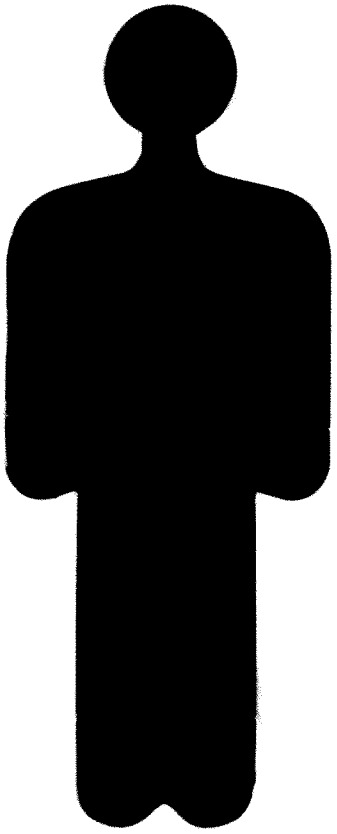
OMNIPAQUE®
(iohexol)
has a
new
image



Introducing

FLEXIPAK™ (Flexible Container)

A new package for OMNIPAQUE with safety, convenience and flexibility built in



The safety package

New FLEXIPAK makes it simple to purge air from the flexible container before hanging to help reduce the potential for air emboli. The easily spiked port eliminates the possibility of infusing microscopic rubber particles from glass-bottle stoppers. And you don't need an air vent because the soft sides collapse as OMNIPAQUE flows.

The convenience package

No more waste and messy cleanups from broken glass bottles. And, FLEXIPAK is ready and easy to hang, even on crowded IV poles. FLEXIPAK lightens the load from setup to administration and all points in between.

The flexibility package

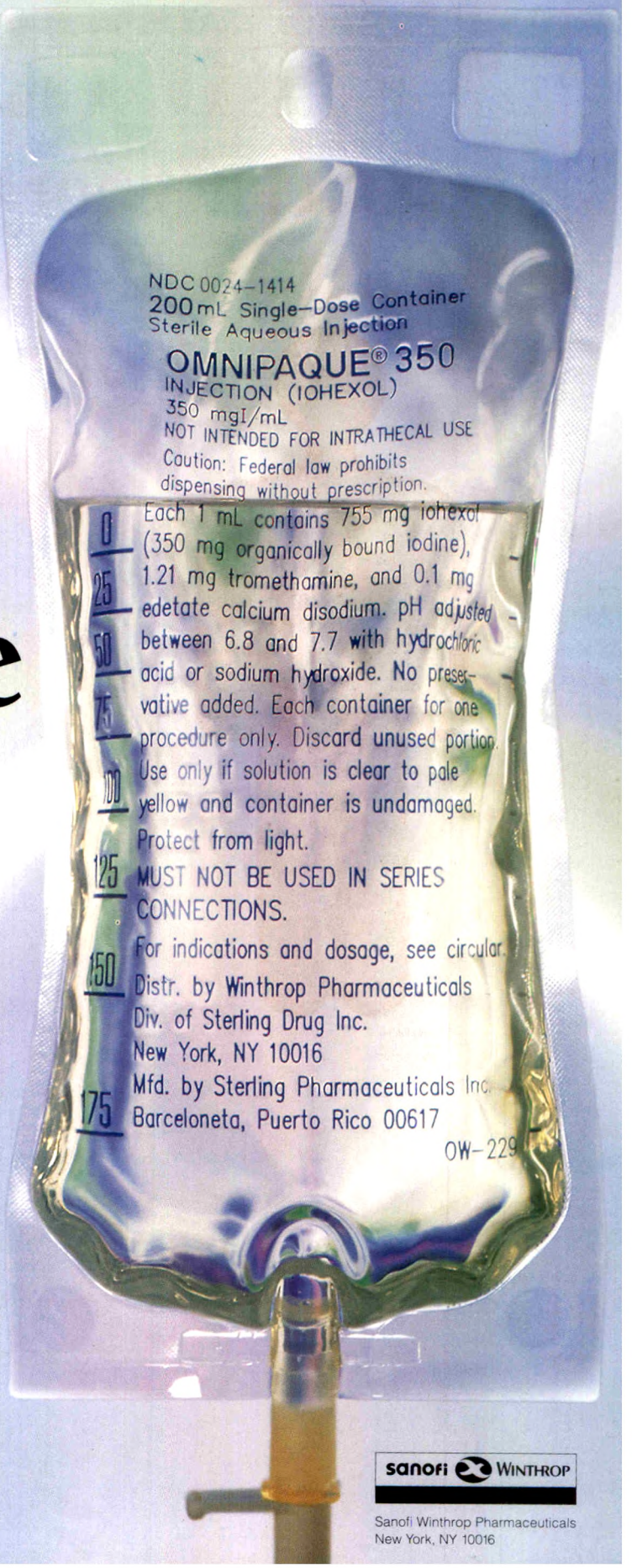
FLEXIPAK is flat and stackable for the best possible utilization of your storage space. And FLEXIPAK is available in the concentrations and sizes used most often.

	100 mL	150 mL	200 mL
OMNIPAQUE 240	X	X	X
OMNIPAQUE 300	X	X	
OMNIPAQUE 350	X	X	X

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It's all part of the package!

NONIONIC
OMNIPAQUE®
(IOHEXOL)



See last page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

All nonionic iodinated contrast media currently available inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary to minimize thromboembolic events.

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Sanofi Winthrop Pharmaceuticals
New York, NY 10016

64-1121

OMNIPAQUE® 140 240 300 350
INJECTION (IOHEXOL)
INTRAVASCULAR

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE USING. A SUMMARY FOLLOWS:

DESCRIPTION: OMNIPAQUE is a sterile, pyrogen-free and preservative-free, nonionic, water-soluble radiographic contrast medium for intravascular administration in concentrations of 140, 240, 300, and 350 mgI/mL. OMNIPAQUE 140 contains 302 mg of iohexol equivalent to 140 mg of organic iodine per mL; OMNIPAQUE 240 contains 518 mg of iohexol equivalent to 240 mg of organic iodine per mL; OMNIPAQUE 300 contains 647 mg of iohexol equivalent to 300 mg of organic iodine per mL; and OMNIPAQUE 350 contains 755 mg of iohexol equivalent to 350 mg of organic iodine per mL. Each milliliter of iohexol solution contains 1.21 mg tromethamine and 0.1 mg edetate calcium disodium with the pH adjusted between 6.8 and 7.7 with hydrochloric acid or sodium hydroxide. Unused portions must be discarded. Iohexol solution is sensitive to light and should be protected from exposure.

CONTRAINDICATIONS: OMNIPAQUE should not be administered to patients with a known hypersensitivity to iohexol.

WARNINGS—General: Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media.

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events. Numerous factors, including length of procedure, catheter and syringe material, underlying disease state, and concomitant medications, may contribute to the development of thromboembolic events. For these reasons, meticulous angiographic techniques are recommended including close attention to guidewire and catheter manipulation, use of manifold systems and/or three-way stopcocks, frequent catheter flushing with heparinized saline solutions and minimizing the length of the procedure. The use of plastic syringes in place of glass syringes has been reported to decrease but not eliminate the likelihood of in vitro clotting.

OMNIPAQUE should be used with extreme care in patients with severe functional disturbances of the liver and kidneys, severe thyrotoxicosis, or myelomatosis. Diabetics with a serum creatinine level above 3 mg/dL should not be examined unless the possible benefits of the examination clearly outweigh the additional risk. OMNIPAQUE is not recommended for use in patients with anuria.

Radiopaque contrast agents are potentially hazardous in patients with multiple myeloma or other paraproteinemia, particularly in those with therapeutically resistant anuria. Although neither the contrast agent nor dehydration has separately proven to be the cause of anuria in myeloma, it has been speculated that the combination of both may be causative factors. The risk in myelomatous patients is not a contraindication; however, special precautions are necessary. Partial dehydration in the preparation of these patients prior to injection is not recommended since this may predispose the patient to precipitation of the myeloma protein in the renal tubules. No form of therapy, including dialysis, has been successful in reversing the effect. Myeloma, which occurs most commonly in persons over age 40, should be considered before instituting intravascular administration of contrast agents.

Ionic contrast media, when injected intravenously or intra-arterially, may promote sickling in individuals who are homozygous for sickle cell disease.

Administration of radiopaque materials to patients known or suspected of having pheochromocytoma should be performed with extreme caution. If, in the opinion of the physician, the possible benefits of such procedures outweigh the considered risks, the procedures may be performed; however, the amount of radiopaque medium injected should be kept to an absolute minimum. The patient's blood pressure should be assessed throughout the procedure and measures for the treatment of hypertensive crisis should be readily available.

Reports of thyroid storm following the use of iodinated, ionic radiopaque contrast media in patients with hyperthyroidism or with an autonomously functioning thyroid nodule suggest that this additional risk be evaluated in such patients before use of any contrast medium.

Urography should be performed with caution in patients with severely impaired renal function and patients with combined renal and hepatic disease.

PRECAUTIONS—General: Diagnostic procedures which involve the use of radiopaque diagnostic agents should be carried out under the direction of personnel with the prerequisite training and with a thorough knowledge of the particular procedure to be performed. Appropriate facilities should be available for coping with any complication of the procedure, as well as for emergency treatment of severe reactions to the contrast agent itself. After parenteral administration of a radiopaque agent, competent personnel and emergency facilities should be available for at least 30 to 60 minutes, since severe delayed reactions have occurred (see ADVERSE REACTIONS: Intravascular—General).

Preparatory dehydration is dangerous and may contribute to acute renal failure in patients with advanced vascular disease, in diabetic patients, and in susceptible nondiabetic patients (often elderly with preexisting renal disease), infants, and small children. Dehydration in these patients seems to be enhanced by the osmotic diuretic action of urographic agents. It is believed that overnight fluid restriction prior to excretory urography generally does not provide better visualization in normal patients. *Patients should be well hydrated prior to and following administration of any contrast medium, including iohexol.*

Acute renal failure has been reported in diabetic patients with diabetic nephropathy and in susceptible nondiabetic patients (often elderly with preexisting renal disease) following excretory urography. Therefore, careful consideration of the potential risks should be given before performing this radiographic procedure in these patients.

Immediately following surgery, excretory urography should be used with caution in renal transplant recipients.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions should always be considered (see ADVERSE REACTIONS: Intravascular—General). It is of utmost importance that a course of action be carefully planned in advance for immediate treatment of serious reactions, and that adequate and appropriate personnel be readily available in case of any reaction.

The possibility of an idiosyncratic reaction in susceptible patients should always be considered (see ADVERSE REACTIONS: Intravascular—General). The susceptible population includes, but is not limited to, patients with a history of a previous reaction to contrast media, patients with a known sensitivity to iodine per se, and patients with a known clinical hypersensitivity: bronchial asthma, hay fever, and food allergies.

The occurrence of severe idiosyncratic reactions has prompted the use of several pretesting methods. However, pretesting cannot be relied upon to predict severe reactions and may itself be hazardous for the patient. It is suggested that a thorough medical history with emphasis on allergy and hypersensitivity, prior to the injection of any contrast media, may be more accurate than pretesting in predicting potential adverse reactions.

A positive history of allergies or hypersensitivity does not arbitrarily contraindicate the use of a contrast agent where a diagnostic procedure is thought essential, but caution should be exercised (see ADVERSE REACTIONS: Intravascular—General). Premedication with antihistamines or corticosteroids to avoid or minimize possible allergic reactions in such patients should be considered and administered using separate syringes. Recent reports indicate that such pretreatment does not prevent serious, life-threatening reactions, but may reduce both their incidence and severity.

Even though the osmolality of OMNIPAQUE is low compared to diatrizoate- or iothalamate-based ionic agents of comparable iodine concentration, the potential transitory increase in the circulatory osmotic load in patients with congestive heart failure requires caution during injection. These patients should be observed for several hours following the procedure to detect delayed hemodynamic disturbances.

General anesthesia may be indicated in the performance of some procedures in selected adult patients; however, a higher incidence of adverse reactions has been reported in these patients and may be attributable to the inability of the patient to identify untoward symptoms, or to the hypotensive effect of anesthesia, which can reduce cardiac output and increase the duration of exposure to the contrast agent.

Angiography should be avoided whenever possible in patients with homocystinuria, because of the risk of inducing thrombosis and embolism.

In angiographic procedures, the possibility of dislodging plaques or damaging or perforating the vessel wall should be borne in mind during the catheter manipulations and contrast medium injection. Test injections to ensure proper catheter placement are recommended.

Selective coronary arteriography should be performed only in those patients in whom the expected benefits outweigh the potential risk. The inherent risks of angiocardiography in patients with chronic pulmonary emphysema must be weighed against the necessity for performing this procedure.

When OMNIPAQUE is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or discoloration is present, do not use.

Information for Patients: Patients receiving injectable radiopaque diagnostic agents should be instructed to:

1. Inform your physician if you are pregnant.
2. Inform your physician if you are diabetic or if you have multiple myeloma, pheochromocytoma, homozygous sickle cell disease, or known thyroid disorder (see WARNINGS—General).
3. Inform your physician if you are allergic to any drugs, food, or if you had any reactions to previous injections of dyes used for x-ray procedures (see PRECAUTIONS—General).
4. Inform your physician about any other medications you are currently taking, including nonprescription drugs, before you are administered this drug.

Drug/Laboratory Test Interaction: If iodine-containing isotopes are to be administered for the diagnosis of thyroid disease, the iodine-binding capacity of thyroid tissue may be reduced for up to 2 weeks after contrast medium administration. Thyroid function tests which do not depend on iodine estimation, eg, T_3 resin uptake or direct thyroxine assays, are not affected. Many radiopaque contrast agents are incompatible in vitro with some antihistamines and many other drugs; therefore, no other pharmaceuticals should be admixed with contrast agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to evaluate carcinogenic potential, mutagenesis, or whether OMNIPAQUE can affect fertility in men or women.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits with up to 100 times the recommended human dose. No evidence of impaired fertility or harm to the fetus has been demonstrated due to OMNIPAQUE. There are, however, no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known to what extent iohexol is excreted in human milk. However, many injectable contrast agents are excreted unchanged in human milk. Although it has not been established that serious adverse reactions occur in nursing infants, caution should be exercised when intravascular contrast media are administered to nursing women. Bottle feedings may be substituted for breast feedings for 24 hours following administration of OMNIPAQUE.

Pediatric Use: Pediatric patients at higher risk of experiencing adverse events during contrast medium administration may include those having asthma, a sensitivity to medication and/or allergens, congestive heart failure, a serum creatinine > 1.5 mg/dL, or those less than 12 months of age.

ADVERSE REACTIONS

Intravascular—General: Adverse reactions following the use of OMNIPAQUE are usually mild to moderate in severity. However, serious, life-threatening, and fatal reactions, mostly of cardiovascular origin, have been associated with the administration of iodine-containing contrast media, including OMNIPAQUE. The injection of contrast media is frequently associated with the sensation of warmth and pain, especially in peripheral angiography; pain and warmth are less frequent and less severe with OMNIPAQUE than with many contrast media.

Cardiovascular System: Arrhythmias including PVCs and PACs (2%), angina/chest pain (1%), and hypotension (0.7%). Others including cardiac failure, asystole, bradycardia, tachycardia, and vasovagal reaction were reported with an individual incidence of 0.3% or less. In controlled clinical trials involving 1,485 patients, one fatality occurred. A cause and effect relationship between this death and iohexol has not been established.

Nervous System: Vertigo [including dizziness and lightheadedness] (0.5%), pain (3%), vision abnormalities [including blurred vision and photomas] (2%), headache (2%), and taste perversion (1%). Others including anxiety, blurred vision, fever, motor and speech dysfunction, convulsion, paresthesia, somnolence, stiff neck, hemiparesis, syncope, shivering, transient ischemic attack, cerebral infarction, and nystagmus were reported, with an individual incidence of 0.3% or less.

Respiratory System: Dyspnea, rhinitis, coughing, and laryngitis, with an individual incidence of 0.2% or less.

Gastrointestinal System: Nausea (2%) and vomiting (0.7%). Others including diarrhea, dyspepsia, cramp, and dry mouth were reported, with an individual incidence of less than 0.1%.

Skin and Appendages: Urticaria (0.3%), purpura (0.1%), abscess (0.1%), and pruritus (0.1%).

Individual adverse reactions which occurred to a significantly greater extent for a specific procedure are listed under that indication in full prescribing information.

Pediatrics: In controlled clinical trials involving 391 patients for pediatric angiocardiography, urography, and contrast-enhanced computed tomographic head imaging, adverse reactions following the use of OMNIPAQUE 240, OMNIPAQUE 300 and OMNIPAQUE 350 were generally less frequent than with adults.

Cardiovascular System: Ventricular tachycardia (0.5%), 2:1 heart block (0.5%), hypertension (0.3%), and anemia (0.3%).
Nervous System: Pain (0.8%), fever (0.5%), taste abnormality (0.5%), and convulsion (0.3%).
Respiratory System: Congestion (0.3%) and apnea (0.3%).
Gastrointestinal System: Nausea (1%), hypoglycemia (0.3%), and vomiting (2%).
Skin and Appendages: Rash (0.3%).

General Adverse Reactions to Contrast Media: Physicians should remain alert for the occurrence of adverse effects in addition to those discussed above. The following reactions have been reported after administration of other intravascular iodinated contrast media, and rarely with iohexol. *Reactions due to technique:* hematomas and ecchymoses. *Hemodynamic reactions:* vein cramp and thrombophlebitis following intravenous injection. *Cardiovascular reactions:* rare cases of cardiac arrhythmias, reflex tachycardia, chest pain, cyanosis, hypertension, hypotension, peripheral vasodilatation, shock, and cardiac arrest. *Renal reactions:* occasionally, transient proteinuria; and rarely, oliguria or anuria. *Allergic reactions:* asthmatic attacks, nasal and conjunctival symptoms, dermal reactions such as urticaria with or without pruritus, as well as pleomorphic rashes, sneezing, and lacrimation; and rarely, anaphylactic reactions. Rare fatalities have occurred due to this or unknown causes. *Signs and symptoms related to the respiratory system:* pulmonary or laryngeal edema, bronchospasm, dyspnea; or *to the nervous system:* restlessness, tremors, convulsions. *Other reactions:* flushing, pain, warmth, metallic taste, nausea, vomiting, anxiety, headache, confusion, pallor, weakness, sweating, localized areas of edema (especially facial cramps), neutropenia, and dizziness. Rarely, immediate or delayed rigors can occur, sometimes accompanied by hyperpyrexia. Infrequently, "iodism" (salivary gland swelling) from organic iodinated compounds appears 2 days after exposure and subsides by the sixth day.

In general, the reactions which are known to occur upon parenteral administration of iodinated contrast agents are possible with any nonionic agent. Approximately 95% of adverse reactions accompanying the use of water-soluble intravascularly administered contrast agents are mild to moderate in degree. However, severe, life-threatening anaphylactoid reactions, mostly of cardiovascular origin, have occurred. Reported incidences of death range from 6.6 per 1 million (0.000066%) to 1 in 10,000 (0.01%). Most deaths occur during injection or 5 to 10 minutes later, the main feature being cardiac arrest, with cardiovascular disease as the main aggravating factor. Isolated reports of hypotensive collapse and shock are found in the literature. The incidence of shock is estimated to be 1 out of 20,000 (0.005%) patients.

Adverse reactions to injectable contrast media fall into two categories: chemotoxic reactions and idiosyncratic reactions.

Chemotoxic reactions result from the physicochemical properties of the contrast media, the dose, and the speed of injection. All hemodynamic disturbances and injuries to organs or vessels perfused by the contrast medium are included in this category.

Idiosyncratic reactions include all other reactions. They occur more frequently in patients 20 to 40 years old. Idiosyncratic reactions may or may not be dependent on the amount of dose injected, the speed of injection, and the radiographic procedure. Idiosyncratic reactions are subdivided into minor, intermediate, and severe. The minor reactions are self-limited and of short duration; the severe reactions are life-threatening and treatment is urgent and mandatory.

The reported incidence of adverse reactions to contrast media in patients with a history of allergy is twice that in the general population. Patients with a history of previous reactions to a contrast medium are three times more susceptible than other patients. However, sensitivity to contrast media does not appear to increase with repeated examinations.

Most adverse reactions to injectable contrast media appear within 1 to 3 minutes after the start of injection, but delayed reactions may occur.

Regardless of the contrast agent employed, the overall estimated incidence of serious adverse reactions is higher with angiocardiography than with other procedures. Cardiac decompensation, serious arrhythmias, angina pectoris, or myocardial ischemia or infarction may occur during angiocardiography and left ventriculography. Electrocardiographic and hemodynamic abnormalities occur less frequently with OMNIPAQUE than with diatrizoate meglumine and diatrizoate sodium injection.

CONSULT PACKAGE INSERT FOR A MORE DETAILED DISCUSSION OF ADVERSE REACTIONS FOR INTRAVASCULAR USE OF OMNIPAQUE.

OVERDOSAGE: Overdosage may occur. The adverse effects of overdosage are life-threatening and affect mainly the pulmonary and cardiovascular systems. The symptoms include cyanosis, bradycardia, acidosis, pulmonary hemorrhage, convulsions, coma, and cardiac arrest. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy.

The intravenous LD_{50} values of OMNIPAQUE (in grams of iodine per kilogram body weight) are 24.2 in mice and 15.0 in rats.

DOSAGE AND ADMINISTRATION: Details are provided in the package insert.

THE RADIOLOGICAL SOCIETY OF NORTH AMERICA
Vanguard Flagship Scholar

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64-1079

mic therapy that was previously thought to be effective. These results suggest that electrophysiologic study results during antiarrhythmic drug therapy exhibit significant day-to-day variability.

1300

Reproducibility of Isoproterenol Tilt-Table Tests in Patients with Syncope

Robert Sheldon, Jan Splawinski, and Shawn Killam

To assess the reproducibility of head-up tilt-table testing, 46 patients each underwent 2 isoproterenol tilt-table tests 1 to 6 weeks apart. The reproducibility of 20 initial negative test results was 85%, and that of 26 initial positive tests was 88%. Symptoms developed monoexponentially with duration of head-up tilt and the time of onset of symptoms during 5 μg/min of isoproterenol correlated well between tests ($r = 0.73$, $p = 0.007$). Of all hemodynamic variables assessed, only trough heart rates correlated well between tests ($r = 0.81$, $p < 0.001$). Thus isoproterenol head-up tilt-table tests are symptomatically reproducible over a period of 1 to 6 weeks. Temporal and hemodynamic variables reproduce well under certain strictly defined conditions.

CONGESTIVE HEART FAILURE

1306

Maintenance of Forearm Vasodilator Action of Atrial Natriuretic Factor in Congestive Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy

Spencer H. Kubo, Steven A. Atlas, John H. Laragh, and Robert J. Cody

To determine if the vasodilator effects of atrial natriuretic factor (ANF) were altered in heart failure, the isolated forearm model was utilized to measure forearm blood flow responses to the intraarterial infusion of ANF using a dose range that was low enough to avoid systemic effects. In control subjects, infusions of 0.5, 1.0, 2.0 and 4.0 μg/min/100 ml forearm volume increased forearm blood flow from 3.21 ± 1.71 to 5.69 ± 3.14, 6.20 ± 2.57, 6.64 ± 2.53 and 6.97 ± 2.49 ml/min/100 ml forearm volume, respectively (all $p < 0.01$). In 7 patients with heart failure, ANF infusion significantly increased forearm blood flow from 2.19 ± 0.98 to 3.18 ± 1.70, 3.76 ± 2.0 and 4.42 ± 2.80 ml/min/100 ml forearm volume for the 0.5, 1.0 and 2.0 μg doses, respectively (all $p < 0.05$). There was no difference in forearm blood flow responses between the 2 groups, expressed as both an absolute response and a percent increase. These data therefore confirm the finding that ANF has a direct vasodilator action in humans and further suggest that ANF-mediated vasodilation is relatively intact in heart failure.

VALVULAR HEART DISEASE

1310
Single-Plane Transesophageal Echocardiography for Assessing Function of Mechanical or Bioprosthetic Valves in the Aortic Valve Position

Dean G. Karalis, Krishnaswamy Chandrasekaran, John J. Ross Jr., Alan Micklin, Bruce M. Brown, Jian-Fang Ren, and Gary S. Mintz

To evaluate the role of transesophageal echocardiography in assessing prosthetic aortic valve function, 89 patients were studied by combined transthoracic and transesophageal echocardiography. Transesophageal echocardiography offered no advantage in the detection and quantification of prosthetic aortic regurgitation unless the transthoracic image quality was poor. Transesophageal echocardiography was limited in detecting mechanical valve obstruction and in detecting aortic regurgitation in the presence of a mechanical mitral valve prosthesis. The value of transesophageal echocardiography was in identifying perivalvular pathology, differentiating perivalvular from valvular regurgitation, and in defining the anatomic abnormality responsible for the prosthetic valve dysfunction. Transesophageal echocardiography should be incorporated with transthoracic echocardiography to provide complete anatomic and hemodynamic assessment of prosthetic aortic valve function.

CONGENITAL HEART DISEASE

1316
Risk of Patent Foramen Ovale for Thromboembolic Events in All Age Groups

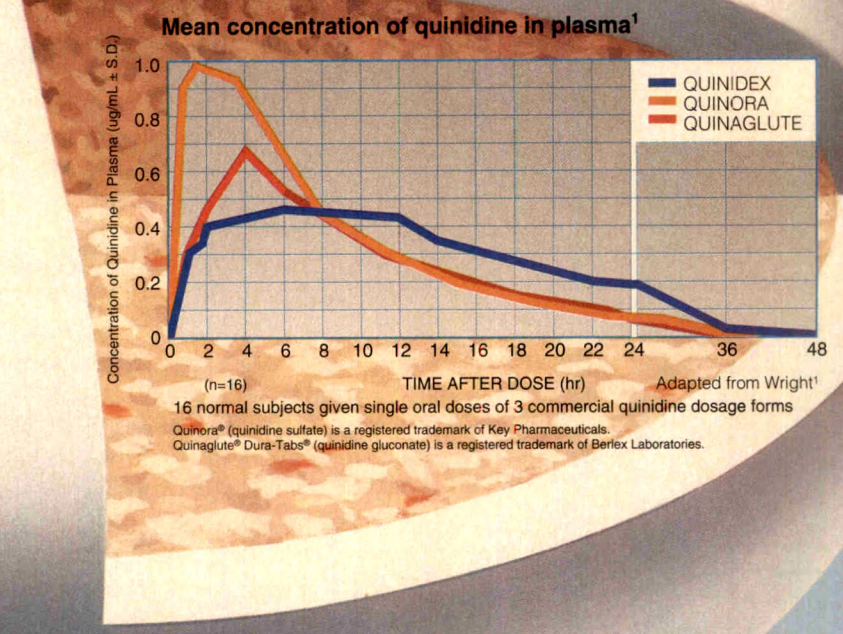
Mark A. de Belder, Leftiris Tourikis, Graham Leech, and A. John Camm

The association between a patent foramen ovale (PFO) and thromboembolic events in young patients has been reported. To assess the role of a PFO in all patients with possible thromboembolic events (regardless of age), precordial and transesophageal contrast echocardiography was performed in 104 consecutive patients (aged 16 to 84 years) presenting with a stroke, transient ischemic attack or peripheral artery embolus (group I); 35 had no risk factor for the event (group Ia), but 69 had a recognized risk factor (group Ib). These studies were also performed in 94 consecutive patients (aged 23 to 82 years) undergoing transesophageal echocardiography for other reasons (group II). The prevalence of a PFO was 26% in group Ia, 14% in Ib, and 3.2% in II (Ia vs II: relative odds 10:1, $p < 0.001$; Ib vs II: relative odds 5:1, $p < 0.02$; and Ia vs Ib: p = not significant). The detection of a PFO was not related to age. The relatively low prevalence of a PFO in this study is discussed. Our data suggest an association between a PFO and thromboembolic event regardless of age, but many patients with a PFO have other risk factors for such events, and this anatomic variant is probably implicated in only a minority.

Continued on page A35

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Quinaglute® Dura-Tabs® (quinidine gluconate) is a registered trademark of Berlex Laboratories.

- Smooth, controlled 24-hour delivery of quinidine sulfate
  Starting dose: One tablet BID for most patients
- Coated tablet for easier swallowing
- Easily identified as Quinidex
- No difference in GI tolerability compared with quinidine gluconate[2]
- The most frequently prescribed quinidine brand[3]

QuinidexExtentabs®

(quinidine sulfate extended-release tablets, USP) 300 mg

Trust experience.

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WYETH-AYERST LABORATORIES
Philadelphia, PA 19101

See brief summary of prescribing information on adjacent page.

A·H·ROBINS

Quinidex Extentabs®

(quinidine sulfate extended-release tablets, USP) 300 mg

Trust experience.

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncracy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heartblock. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4–8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: *General*—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients—As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug	Effect
Quinidine with anticholinergic drugs	Additive vagolytic effect
Quinidine with cholinergic drugs	Antagonism of cholinergic effects
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics	Alkalinization of urine resulting in decreased excretion of quinidine
Quinidine with coumarin anticoagulants	Reduction of clotting factor concentrations
Quinidine with tubocurare, succinylcholine and decamethonium	Potentiation of neuromuscular blockade
Quinidine with phenothiazines and reserpine	Additive cardiac depressive effects
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)	Decreased plasma half-life of quinidine
Quinidine with digoxin	Increased serum concentration of digoxin (See Warnings)
Quinidine with amiodarone	Increased serum concentration of quinidine
Quinidine with cimetidine	Prolonged quinidine half-life and an increase in serum quinidine level
Quinidine with ranitidine	Premature ventricular contractions and/or bigeminy
Quinidine with verapamil	Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Quinidine with nifedipine	Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy. Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Labor and Delivery—There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers—Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otologic—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential neutropenia.

Immunologic—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Rev. October 1987

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1321
Minimally Invasive Management of Transposition of the Great Arteries in the Newborn Period
Cameron J. B. Ward, Richard E. Hawker, Stephen G. Cooper, David Brieger, Graham Nunn, Timothy B. Cartmill, John M. Celermajer, and Gary F. Sholler

This study reports on a predominantly noninvasive management program for neonatal transposition of the great arteries incorporating balloon atrial septostomy (BAS) under echocardiographic control. BAS was performed via the umbilicus using echocardiographic control in 17 patients (85% of patients in whom this approach was attempted), and proved safe and effective. Thirteen patients did not require ventilation during BAS. There were minimal complications and satisfactory septostomies in all cases. Intracardiac and coronary anatomy were correctly predicted by echocardiography. Without diagnostic cardiac catheterization 9 patients underwent neonatal arterial switch procedures and 2 underwent palliative procedures.

1325
Decreased Plasma Atriopeptin Response to Volume-Overloading Maneuvers and Exercise After Atriopulmonary Anastomosis of Fontan
Hélène Perrault, Joaquim Miró, André Davignon, Mireille Béland, Beth Armstrong, Gaétan Thibault, Marc Cantin, and Claude Chartrand

After the Fontan operation, patients have a chronic pressure-volume overload, and salt and water retention are frequent clinical observations. The hypothesis that this abnormal hydro-mineral status could be related to an inability of right atrial cardiocytes to increase already elevated atriopeptin (ANP) levels in response to further volume overload, and thus reduce the potential for diuresis and natriuresis, was examined. Patients were submitted to a 10° head-down tilt during routine cardioangiography, and at another time to a graded maximal exercise protocol. Plasma ANP levels were increased (114 ± 10 pg/ml) at basal conditions and did not increase in response to tilting or angiography, despite significant increases in mean right atrial pressure (basal: 12 ± 0.7 mm Hg; tilt: 13.4 ± 0.7 mm Hg; and after angiography: 15.8 ± 0.8 mm Hg). Maximal exercise resulted in only a slight increase in circulating ANP in patients compared with a threefold increase in healthy control subjects. The results suggest an attenuated stimulus-release response for ANP in Fontan patients, which could have clinical implications in fluid-balance regulation.

MISCELLANEOUS

1329

Major Electrocardiographic Abnormalities in Persons Aged 65 Years and Older (the Cardiovascular Health Study)

Curt D. Furberg, Teri A. Manolio, Bruce M. Psaty, Diane E. Bild, Nemat O. Borhani, Anne Newman, Bernard Tabatznik, and Pentti M. Rautaharju, for the Cardiovascular Health Study Collaborative Research Group

The prevalence of major electrocardiographic abnormalities was determined in 5,150 adults aged ≥65 years from the Cardiovascular Health Study, a study of risk factors for stroke and coronary heart disease in the elderly. Ventricular conduction defects, major Q/QS waves, left ventricular hypertrophy, isolated major ST-T-wave abnormalities, atrial fibrillation and first-degree atrioventricular block were collectively categorized as major electrocardiographic abnormalities. Prevalence of any major electrocardiographic abnormality was 29% in the entire cohort; 19% among 2,413 participants who reported no history of coronary artery disease or systemic hypertension, and 37% among 2,737 with history of coronary artery disease or hypertension. Prevalence of major electrocardiographic abnormalities was higher in men than in women regardless of history and tended to increase with age. Major Q/QS waves were found in 5.2%, and more than half were in subjects who did not report a previous myocardial infarction. Major electrocardiographic abnormalities are common in elderly men and women irrespective of the history of heart disease.

1336

Normalization of Upright Exercise Hemodynamics and Improved Exercise Capacity One Year After Orthotopic Cardiac Transplantation

Laszlo Rudas, Peter W. Pflugfelder, F. Neil McKenzie, Alan H. Menkis, Richard J. Novick, and William J. Kostuk

To assess the contribution of cardiac changes to improvement in exercise capacity, the serial evolution of upright rest and exercise hemodynamics was studied in 17 patients at 3 and 12 months after heart transplantation. Heart rate responsiveness, reflected by rapid heart rate acceleration on sitting and rapid deceleration after exercise, developed in the first year. Pulmonary capillary wedge and right atrial pressures were lower at 1 year, both at rest and at peak exercise. Cardiac index at peak exercise was greater at 12 months, mediated primarily by higher exercise heart rate. In the first year after heart transplantation, improved rest and exercise hemodynamics and heart rate responsiveness contribute significantly to the improved functional capacity observed in these patients.

Continued on page A38

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* REFERENCES
1. N Engl J Med 1989;321:129-35. 2. Aust-Fam-Physician. 1990 Feb; 19(2)217221-3. 3. American Fam-Physician r. v43 p1431 April 91. 4. New Scientist v119 p24 Aug 25 88. 5. Health (N.Y., N.Y.) v20 p8 May88. 6. JAMA v257 p2134-5 April 24, 87. 7. N. Engl J Med v311 p1206-11 Nov. 8 84. 8.JAMA, July 24/31 V266 No. 4.

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1340
Dependency of Arterial Compliance on Circulating Neuroendocrine and Metabolic Factors in Normal Subjects
Joel M. Neutel, David H. G. Smith, William F. Graettinger, and Michael A. Weber

To evaluate whether arterial compliance is influenced by neuroendocrine and metabolic factors, proximal (aorta and large arteries) and distal compliance (small arteries and arterioles) was measured in 57 volunteers (30 hypertensive and 27 normotensive). Proximal compliance correlated with plasma insulin, norepinephrine, triglycerides, total cholesterol and high-density lipoprotein (HDL) cholesterol. Distal compliance correlated with insulin, triglycerides, total cholesterol and lower HDL cholesterol. Patients with reduced proximal compliance had higher levels of insulin, plasma renin activity, triglycerides, total cholesterol and lower HDL levels than patients with normal compliance. These findings suggest that such humoral factors as catecholamines, the renin system, lipids and insulin may be linked to morphologic changes that decrease arterial compliance.

1345
Slope of the End-Systolic Pressure-Volume Relation Derived from Single Beat Analysis Is Not Always Sensitive to Positive Inotropic Stimuli in Humans
Tomoyuki Iwase, Tetsuya Tomita, Shinji Miki, Kunihiko Nagai, and Tomoyuki Murakami

Single beat estimation of the slope of the end-systolic pressure-volume relation assumes symmetric left ventricular pressure increase and decay, and requires extrapolation of peak isovolumic developed pressure (Pmax). To test the sensitivity of this slope to positive inotropic stimuli, biplane cineangiocardiography and simultaneous high-fidelity left ventricular pressure measurements were performed under baseline conditions and during norepinephrine infusion or after postextrasystolic potentiation in 50 patients with heart disease. Left ventricular pressure increase and decay were asymmetric after postextrasystolic potentiation. The slope increased during norepinephrine infusion and decreased after postextrasystolic potentiation. It showed a high correlation with estimated Pmax ($r = 0.86$). In conclusion, the slope of the end-systolic pressure-volume relation derived from single beat analysis is not always sensitive to inotropic interventions. Its sensitivity is highly dependent on the accuracy of extrapolation of Pmax, and this assessment of contractile state is limited especially when isovolumic contraction and relaxation are dissociated.

METHODS

1354
Validity of Cardiac Output Measurement by Computer-Averaged Impedance Cardiography, and Comparison with Simultaneous Thermodilution Determinations
Brian R. Pickett and James C. Buell

The accuracy and reproducibility of cardiac output measurement by ensemble-averaged computerized impedance cardiography were compared

Continued on page A44

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INTRODUCING

NEW ZOCOR™ ONCE-A-DAY (SIMVASTATIN)



An HMG-CoA reductase inhibitor for a wide range of patients with primary hypercholesterolemia (Types IIa and IIb) as an adjunct to diet

For a Brief Summary of Prescribing Information, please see the last page of this advertisement.

For many patients
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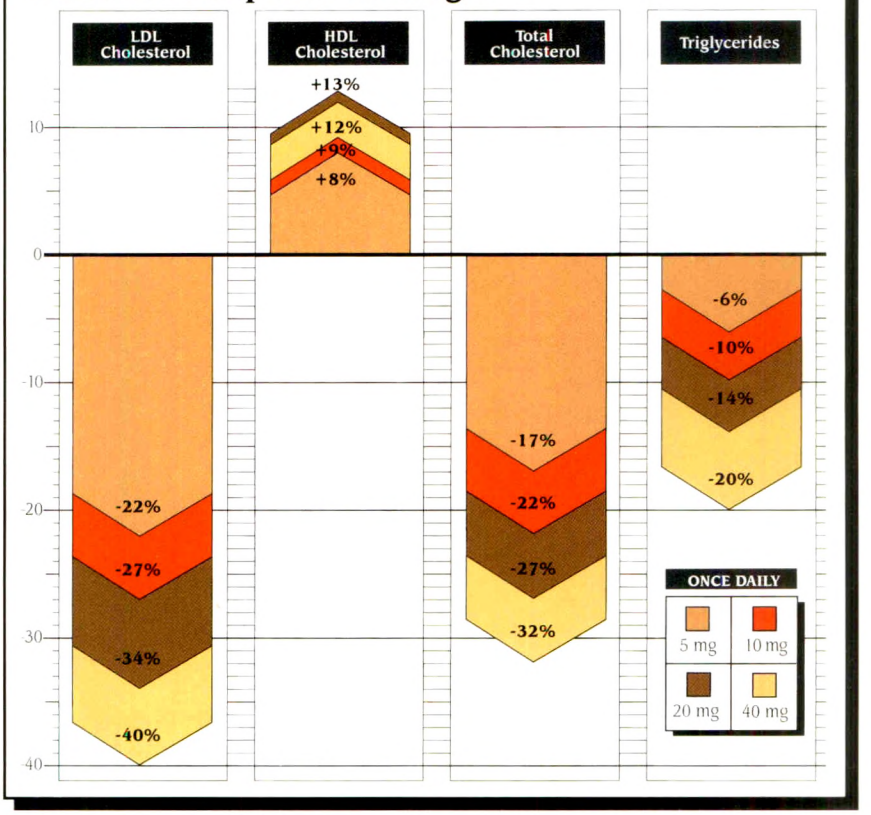
THE EFFICACY THAT YOU NEED

Working to achieve your high standards for lowering cholesterol

In indicated patients,

A positive effect on all key lipid parameters

Overall mean percent changes*,**



The recommended starting dose is 5 or 10 mg once a day in the evening. Patients with LDL cholesterol levels (on diet) >190 mg/dL should be started on 10 mg once a day. A starting dose of 5 mg once a day should be considered for patients with LDL cholesterol (on diet) of ≤190 mg/dL and for elderly patients. For more information about dosage, including dosage in patients who are on concomitant immunosuppressive therapy or in patients with severe renal insufficiency, see full Prescribing Information.

ZOCOR is contraindicated in patients who are hypersensitive to any component of the medication; in patients with active liver disease or unexplained persistent transaminase elevations (see WARNINGS); in pregnant or lactating patients; and in women of childbearing age except when such patients are highly unlikely to conceive. For additional details, including information about liver function testing and myopathy, see full Prescribing Information.

* Mean percent changes from baseline from two randomized controlled trials of 6 to 8 weeks' duration in 95 patients receiving ZOCOR 5 mg once daily. In these studies, mean baseline cholesterol levels (on diet) were 209 mg/dL for LDL cholesterol and 288 mg/dL for total cholesterol.

** Mean percent changes from baseline from six randomized controlled trials of 4 to 12 weeks' duration in 767 patients receiving ZOCOR 10, 20, or 40 mg once daily. In these studies, mean baseline cholesterol levels (on diet) were 277 mg/dL for LDL cholesterol and 354 mg/dL for total cholesterol.

For a Brief Summary of Prescribing Information, please see the next page of this advertisement.

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For a wide range of patients with primary hypercholesterolemia (Types IIa and IIb), after an adequate trial of diet and other nondrug therapy,

NEW ZOCOR™ ONCE-A-DAY (SIMVASTATIN)



ONCE-A-DAY

ZOCOR

SIMVASTATIN

ZOCOR is available in 5-mg, 10-mg, 20-mg, and 40-mg tablet strengths.

CONTRAINDICATIONS: Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of HMG-CoA reductase inhibitors such as ZOCOR® (Simvastatin) to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, ZOCOR may cause fetal harm when administered to a pregnant woman. Therefore, simvastatin is contraindicated during pregnancy and in nursing mothers. **Simvastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If a patient becomes pregnant while taking this drug, simvastatin should be discontinued and the patient should be apprised of the potential hazard to the fetus.

WARNINGS: ***Liver Dysfunction:*** **Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases have occurred in 1% of patients who received simvastatin in clinical trials.** When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

It is recommended that liver function tests be performed during therapy with simvastatin. Serum transaminase levels, including ALT (SGPT), should be monitored before treatment begins, every 6 weeks for the first 3 months, every 8 weeks during the remainder of the first year, and periodically thereafter (e.g., at approximately 6-month intervals). Special attention should be paid to patients who develop elevated serum transaminase levels, and in these patients, measurements should be repeated promptly and then performed more frequently. If the transaminase levels show evidence of progression, particularly if they rise to 3 times the upper limit of normal and are persistent, the drug should be discontinued. Liver biopsy should be considered if elevations persist beyond the discontinuation of the drug.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3 times the upper limit of normal) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms, and did not require interruption of treatment.

Skeletal Muscle: Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been associated with simvastatin therapy. Rhabdomyolysis has also been associated with other HMG-CoA reductase inhibitors when they were administered alone or concomitantly with 1) immunosuppressive therapy, including cyclosporine in cardiac transplant patients; 2) gemfibrozil or lipid-lowering doses (≥1 g/day) of nicotinic acid in non-transplant patients; or 3) erythromycin in seriously ill patients. Some of the patients who had rhabdomyolysis in association with the reductase inhibitors had preexisting renal insufficiency, usually as a consequence of longstanding diabetes. In most subjects who have had an unsatisfactory lipid response to either simvastatin or gemfibrozil alone, the possible benefits of combined therapy with these drugs are not considered to outweigh the risk of severe myopathy, rhabdomyolysis, and acute renal failure. While it is not known whether this interaction occurs with fibrates other than gemfibrozil, myopathy and rhabdomyolysis have occasionally been associated with the use of other fibrates alone, including clofibrate. Therefore, the combined use of simvastatin with other fibrates should generally be avoided.

Physicians contemplating combined therapy with simvastatin and lipid-lowering doses of nicotinic acid or with immunosuppressive drugs should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy.

Because of an apparent relationship between myopathy and increased plasma levels of active metabolites derived from other HMG-CoA reductase inhibitors, the daily dosage should not exceed 10 mg/day in patients who are taking cyclosporine (see DOSAGE AND ADMINISTRATION in Prescribing Information).

Simvastatin therapy should be temporarily withheld or discontinued in any patient who has an acute, serious condition suggestive of a myopathy or who has a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, and uncontrolled seizures).

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Simvastatin therapy should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected.

PRECAUTIONS: ***General:*** Before instituting therapy with ZOCOR, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients and to treat other underlying medical problems (see INDICATIONS AND USAGE in Prescribing Information).

Simvastatin may cause elevation of CPK and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with simvastatin.

Homozygous Familial Hypercholesterolemia: ZOCOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin:* See WARNINGS, *Skeletal Muscle*.

Antipyrine: Because simvastatin had no effect on the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected.

Propranolol: In healthy male volunteers, there was a significant decrease in mean C_{max}, but no change in AUC, for simvastatin total and active inhibitors with concomitant administration of single doses of ZOCOR® (Simvastatin) and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolol were not affected.

Digoxin: Concomitant administration of a single dose of digoxin in healthy male volunteers receiving simvastatin resulted in a slight elevation (less than 0.3 ng/mL) in digoxin concentrations in plasma (as measured by a radioimmunoassay) compared to concomitant administration of placebo and digoxin. Patients taking digoxin should be monitored appropriately when simvastatin is initiated.

Warfarin: Simvastatin therapy appeared to enhance slightly the anticoagulant effect of warfarin (mean changes in prothrombin time less than 2 seconds) in normal volunteers maintained in a state of low therapeutic anticoagulation. With other reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Other Concomitant Therapy: Although specific interaction studies were not performed, in clinical studies, simvastatin was used concomitantly with angiotensin-converting-enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions. The effect of cholestyramine on the absorption and kinetics of simvastatin has not been determined.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. However, clinical studies have shown that simvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve and does not reduce basal plasma testosterone concentration (see CLINICAL PHARMACOLOGY, *Clinical Studies* in Prescribing Information). Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG; the effect of simvastatin on HCG-stimulated testosterone secretion has not been studied.

Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with simvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients who are also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 44 times higher than the mean drug level in humans taking 40 mg/day.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits, and necrosis of small vessels, were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced plasma drug levels that were about 50 times higher than the mean drug levels in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 3, 15, and 33 times higher than the mean human plasma drug concentration (as total inhibitory activity) after a 40-mg oral dose. Liver carcinomas were significantly increased in high-dose females and in mid- and high-dose males, with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day. Although mice were given up to 500 times the human dose (HD) on a mg/kg body weight basis, blood levels of HMG-CoA reductase inhibitory activity were only 3 to 33 times higher in mice than in humans given 40 mg of ZOCOR.

In a separate 92-week carcinogenicity study in mice at doses of up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed. Although mice were given up to 31 times the human dose on a mg/kg basis, plasma drug levels were only 2 to 4 times higher than in humans given 40 mg simvastatin as measured by AUC.

In a 2-year study in rats, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 45 times higher levels of simvastatin than humans given 40 mg simvastatin (as measured by AUC). Preliminary results from a second 2-year rat study indicate an increase in the incidence of thyroid and liver tumors in male and female rats at doses that produce exposure levels ≥29 times (based on AUC) those achieved in humans at a dosage of 40 mg/day. Liver tumors are found in rodents with all the chemically similar drugs of this class. No increased incidence of tumors was observed at doses that produce exposure levels 15 times (based on AUC) those seen in man.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (15 times the maximum human exposure level, based on AUC, in patients receiving 40 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day (which produces exposure levels 44 times higher than those in humans taking 40 mg/day), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation at 10 mg/kg/day (approximately 7 times the human exposure level, based on AUC, at 40 mg/day). The clinical significance of these findings is unclear.

Pregnancy: *Pregnancy Category X.* See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Simvastatin was not teratogenic in rats at doses of 25 mg/kg/day or in rabbits at doses of up to 10 mg/kg daily. These doses resulted in 6 times (rat) or 4 times (rabbit) the human exposure based on mg/m² surface area. However, in studies with another structurally related HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. Simvastatin should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If a woman becomes pregnant while taking simvastatin, it should be discontinued and the patient should be advised again as to the potential hazards to the fetus.

Nursing Mothers: It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in children and adolescents have not been established. Because children and adolescents are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of children or adolescents with simvastatin is not recommended at this time.

ADVERSE REACTIONS: In the controlled clinical studies and their open extensions (2,423 patients with mean duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse experiences attributable to ZOCOR® (Simvastatin). Adverse reactions have usually been mild and transient. ZOCOR has been evaluated for serious adverse reactions in more than 21,000 patients and is generally well tolerated.

Clinical Adverse Experiences: Adverse experiences occurring at an incidence of 1% or greater in patients treated with ZOCOR, regardless of causality, in controlled clinical studies are shown in the table below:

	ZOCOR (N=1,583)	Placebo (N=157)	Cholestyramine (N=179)	Probucol (N=81)
Body as a Whole				
Abdominal pain	3.2%	3.2%	8.9%	2.5%
Asthenia	1.6	2.5	1.1	1.2
Gastrointestinal				
Constipation	2.3	1.3	29.1	1.2
Diarrhea	1.9	2.5	7.8	3.7
Dyspepsia	1.1	—	4.5	3.7
Flatulence	1.9	1.3	14.5	6.2
Nausea	1.3	1.9	10.1	2.5
Nervous System/Psychiatric				
Headache	3.5	5.1	4.5	3.7
Respiratory				
Upper respiratory infection	2.1	1.9	3.4	

The following effects have been reported with drugs in this class:

Skeletal: Myopathy, rhabdomyolysis, arthralgias.

Neurological: Dysfunction of certain cranial nerves (including alteration of taste, impairment of extraocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: Pancreatitis; hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia; vomiting.

Skin: Alopecia.

Reproductive: Gynecomastia, loss of libido, erectile dysfunction.

Eye: Progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: Elevated transaminases, alkaline phosphatase, and bilirubin; thyroid function abnormalities.

Laboratory Tests: Marked persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 5% of patients had elevations of CPK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CPK. Muscle pain or dysfunction usually was not reported (see WARNINGS, *Skeletal Muscle*).

Concomitant Therapy: In controlled clinical studies in which simvastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with simvastatin or cholestyramine. The combined use of simvastatin with fibrates should generally be avoided (see WARNINGS, *Skeletal Muscle*).

OVERDOSAGE: Significant lethality was observed in mice after a single oral dose of 9 g/m². No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m², respectively. No specific diagnostic signs were observed in rodents. At these doses, the only signs seen in dogs were emesis and mucoid stools.

There have been no cases of clinically significant overdosage with ZOCOR in humans. Until further experience is obtained, no specific treatment of overdosage with ZOCOR can be recommended.

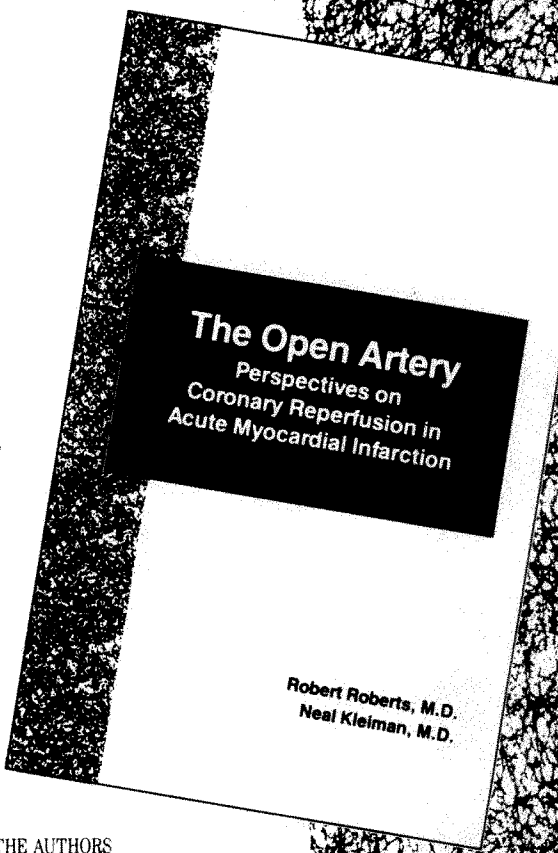
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For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of MERCK & CO., Inc., West Point, PA 19486 ©ZZ007(901)

As a companion to the Sobel and Hirsh **Coronary Thrombolysis and Conjunctive Treatment: Principles and Practice,** add Roberts and Kleiman's **The Open Artery: Perspectives on Coronary Reperfusion in Acute Myocardial Infarction** to your reference library today.

EVOLVING ISSUES IN ACUTE MYOCARDIAL INFARCTION:

CORONARY REPERFUSION — A Question Of Timing



Although now accepted as a standard in the treatment of acute myocardial infarction, reperfusion therapy continues to generate much controversy. Most recently, debate has centered on the value of reperfusion at different stages in the evolution of infarction.

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- The relationship between a patent coronary artery following acute infarction and short- and long-term mortality;
- The GUSTO trial and implications for the future; and
- The "open artery hypothesis" and mechanisms thorough which late reperfusion may product long-term improvement in morbidity and mortality.

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Neal Kleiman, M.D.
Assistant Professor of Medicine, Section of Cardiology, Baylor College of Medicine; Director – Cardiac Catheterization Laboratories, Methodist Hospital, Houston, Texas

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with those of simultaneously performed thermodilution cardiac output determinations; 201 paired estimates from 43 patients were compared by Pearson correlation coefficients and agreement between methods. Paired impedance and thermodilution values correlated well ($r = 0.75$; $p < 0.0001$). Correlation was improved when mean impedance was compared with mean thermodilution in each patient ($r = 0.86$; $p < 0.0001$). Agreement between methods was high. Impedance cardiac output is noninvasive, and essentially equivalent in accuracy and reproducibility to thermodilution cardiac output.

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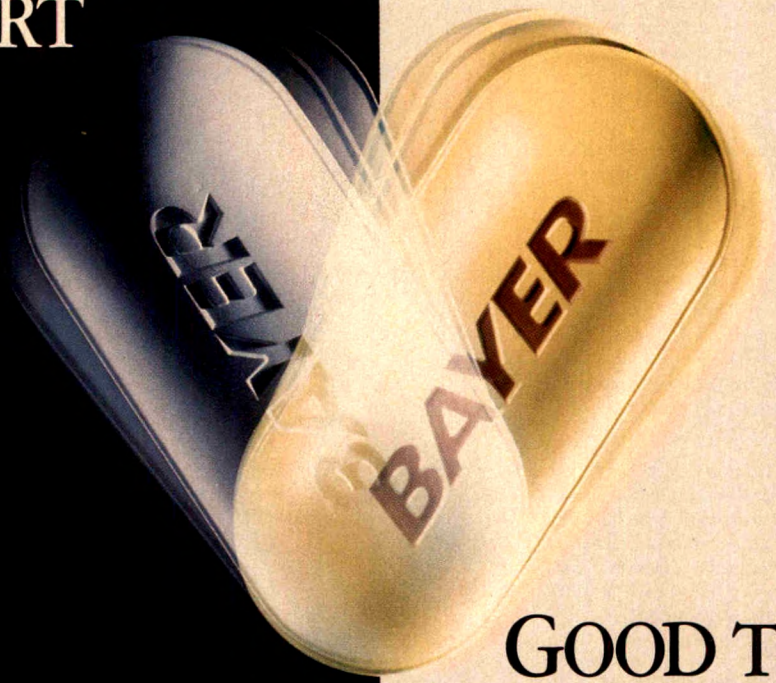
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Continued on page A51

PROPHYLAXIS POST-MI AND IN UNSTABLE ANGINA

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GOOD TO THE STOMACH.

Safety-coated Therapy BAYER® ENTERIC: An ideal choice for second MI prophylaxis.

Therapy BAYER® ENTERIC is an excellent way to take 100% pure BAYER® aspirin for the long term. That's because the enteric coating ensures that the delayed-release caplet dissolves only in the intestine, minimizing your patients' risk of gastric irritation.

Therapy BAYER® ENTERIC is also economically priced to cost less than Ecotrin®. So it's a recommendation that can save your patients dollars — while making good sense.



Tell your patients to look for the new Therapy BAYER® ENTERIC box with the green shield.

THERAPY FOR LIFE.

Please see Brief Summary of Prescribing Information on the following page.

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BRIEF SUMMARY

Therapy BAYER® ENTERIC Aspirin

Delayed-Release Enteric Aspirin (Acetylsalicylic Acid) Caplets to Help Reduce the Risk of Second MI or MI in Unstable Angina

DOSAGE AND ADMINISTRATION:

Although most of the studies used dosages exceeding 300 mg, two trials used only 300 mg daily, and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 mg or a conventional 325 mg aspirin dose daily is a reasonable routine dose that would minimize gastrointestinal adverse reactions. This use of aspirin applies to both solid oral dosage forms (buffered and plain aspirin) and buffered aspirin in solution.

CARDIOVASCULAR AND BIOCHEMICAL:

In the AMIS trial, the dosage of 1,000 mg per day of aspirin was associated with small increases in systolic blood pressure (BP) (average 1.5 to 2.1 mm) and diastolic BP (0.5 to 0.6 mm), depending upon whether maximal or last available readings were used. Blood urea nitrogen and uric acid levels were also increased but by less than 1.0 mg percent. Subjects with marked hypertension or renal insufficiency had been excluded from the trial so that the clinical importance of these observations for such subjects or for any subjects treated over more prolonged periods is not known. It is recommended that patients placed on long-term aspirin treatment, even at doses of 300 mg per day, be seen at regular intervals to assess changes in these measurements.

BIOAVAILABILITY:

A single-dose bioavailability study[1] has demonstrated that plasma acetylsalicylic acid and salicylic acid concentrations resulting from Therapy BAYER® ENTERIC are equivalent to those from plain aspirin, i.e., non-enteric-coated aspirin. As expected, the enteric coating on Therapy BAYER® ENTERIC results in delayed absorption (peak achieved at approximately five hours postdosing) relative to plain aspirin. Dissolution of the enteric coating occurs at neutral-to-basic pH and is therefore dependent on gastric emptying into the duodenum. With continued dosing, appropriate therapeutic plasma levels are maintained.

SAFETY:

The safety of enteric-coated aspirin has been demonstrated in a number of endoscopic studies comparing enteric-coated aspirin and plain aspirin, as well as plain buffered and "arthritis strength" preparations. In these studies, endoscopies were performed in healthy volunteers before and after either two-day or 14-day administration of aspirin doses of 3,900 or 4,000 mg per day. Compared to all the other preparations, the enteric-coated aspirin produced significantly less damage to the gastric mucosa. There was also statistically less duodenal damage when compared with the plain, i.e., non-enteric-coated, aspirin.

ADVERSE REACTIONS:

Gastrointestinal reactions: Doses of 1,000 mg per day of aspirin caused gastrointestinal symptoms and bleeding that, in some cases, were clinically significant. In the largest postinfarction study (the Aspirin Myocardial Infarction Study [AMIS] with 4,500 people),[2] the percentage of incidences of gastrointestinal symptoms for the aspirin (1,000 mg of a standard, solid-tablet formulation) and placebo-treated subjects, respectively, were stomach pain (14.5%, 4.4%), heartburn (11.9%, 4.8%), nausea and/or vomiting (7.6%, 2.1%), and hospitalization for GI disorder (4.9%, 3.5%). In the AMIS and other trials, aspirin-treated patients had increased rates of gross gastrointestinal bleeding. Symptoms and signs of gastrointestinal irritation were not significantly increased in subjects treated for unstable angina with buffered aspirin in solution.

PROFESSIONAL WARNING:

Occasional reports have documented individuals with impaired gastric emptying in whom there may be retention of one or more enteric-coated aspirin caplets over time. This phenomenon may occur as a result of outlet obstruction from ulcer disease alone or combined with hypotonic gastric peristalsis. Because of the integrity of the enteric coating in an acidic environment, these caplets may accumulate and form a bezoar in the stomach. Individuals with this condition may present with complaints of early satiety or of vague upper abdominal distress. Diagnosis may be made by endoscopy or by abdominal films, which show opacities suggestive of a mass of small caplets.[3] Management may vary according to the condition of the patient. Options include gastrotomy and alternating slightly basic and neutral lavage.[4] While there have been no clinical reports, it has been suggested that such individuals may also be treated with parenteral cimetidine (to reduce acid secretion) and then given sips of slightly basic liquids to effect gradual dissolution of the enteric coating. Progress may be followed with plasma salicylate levels or via recognition of tinnitus by the patient.

It should be kept in mind that individuals with a history of partial or complete gastrectomy may produce reduced amounts of acid and therefore have less acidic gastric pH. Under these circumstances, the benefits offered by the acid-resistant enteric coating may not exist.

REFERENCES:

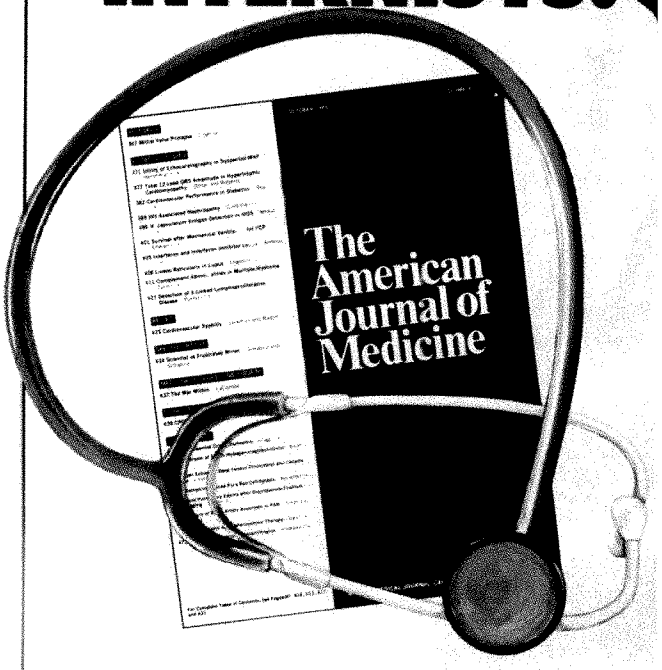
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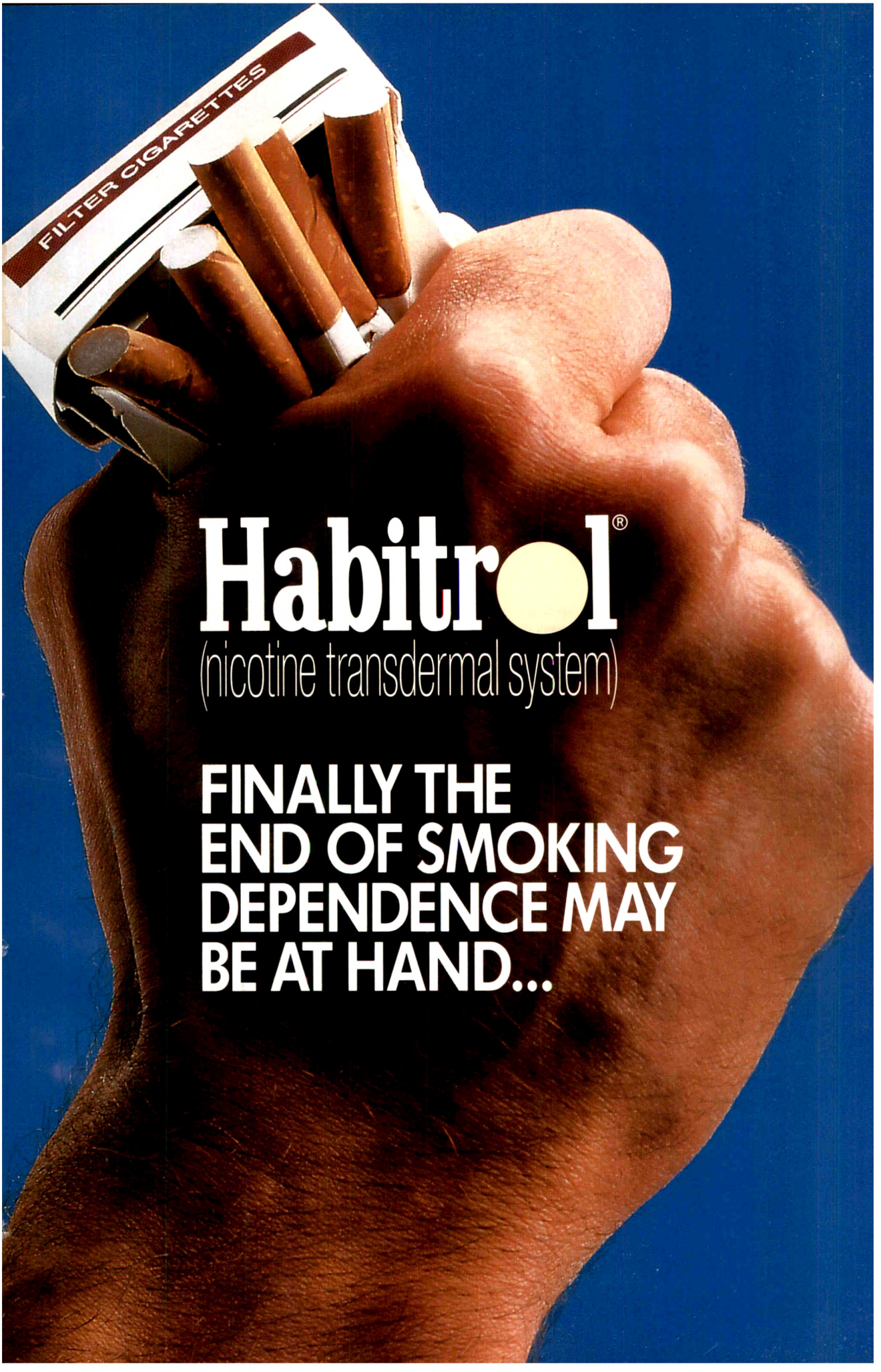
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FILTER CIGARETTES
Habitrol®
(nicotine transdermal system)
FINALLY THE END OF SMOKING DEPENDENCE MAY BE AT HAND...

For the motivated patient who wants to quit



Habitrol®
(nicotine transdermal system)

Habitrol significantly increases abstinence rates* when used as part of a comprehensive behavioral smoking cessation program—even in moderately to highly nicotine-dependent patients[1†]

- Significantly reduces craving for cigarettes through controlled nicotine release[1]
- Helps break the chain of smoking dependence with full 24-hour nicotine plasma levels
- Safe and well tolerated
- Provides the safety of child-resistant packaging

Habitrol is available with a Patient Support Kit, to be used as part of a comprehensive behavioral smoking cessation program. This kit provides materials to help motivated patients address the behavioral and social components of smoking dependence.

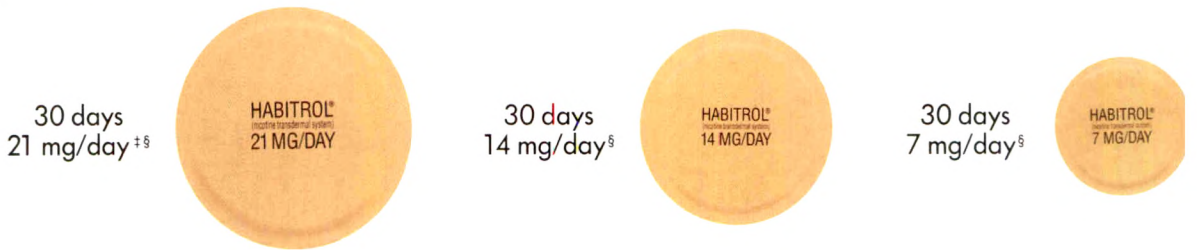
This product should not be used for more than three months. The effects of Habitrol treatment on fetal development are unknown. Pregnant or nursing smokers should be encouraged to attempt smoking cessation using nonpharmacologic approaches before using Habitrol. The risks vs. benefits of nicotine replacement should be weighed in patients with certain cardiovascular and peripheral vascular diseases. Certain concomitant medications may need dosage adjustments (see Drug Interactions section of complete Prescribing Information).

THE PATCH THAT BEATS THE PACK



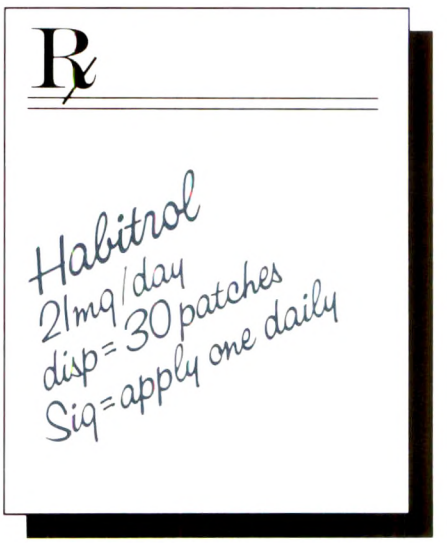
Helps patients adjust to a smokefree lifestyle with gradual reduction of nicotine

- Available in three dosages for step-down therapy
- Start most patients on one 21 mg/day patch for 30 days, continue with one 14 mg/day patch for 30 days, and follow with one 7 mg/day patch for 30 days‡



Treatment Range	4-8 weeks	2-4 weeks	2-4 weeks

- Used and unused systems should be kept out of the reach of children and pets



*Abstinence was measured by diary entries and confirmed by breath carbon monoxide levels.
†Represents patients scoring ≥6 points on the Fagerstrom Tolerance Test
‡For patients with coronary artery disease or who weigh less than 100 lbs or smoke less than ½ pack of cigarettes/day, please see Individualization of Dosage Section of Prescribing Information
§Patches shown 50% of actual size

Please see brief summary of Prescribing Information on next page.

Habitrol®
(nicotine transdermal system)
Systemic delivery of 21, 14, or 7 mg/day over 24 hours

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Habitrol treatment is indicated as an aid to smoking cessation for the relief of nicotine withdrawal symptoms. Habitrol treatment should be used as a part of a comprehensive behavioral smoking cessation program.

The use of Habitrol systems for longer than 3 months has not been studied.

CONTRAINDICATIONS
Use of Habitrol systems is contraindicated in patients with hypersensitivity or allergy to nicotine or to any of the components of the therapeutic system.

WARNINGS
Nicotine from any source can be toxic and addictive. Smoking causes lung cancer, heart disease, emphysema, and may adversely affect the fetus and the pregnant woman. For any smoker, with or without concomitant disease or pregnancy, the risk of nicotine replacement in a smoking cessation program should be weighed against the hazard of continued smoking while using Habitrol systems, and the likelihood of achieving cessation of smoking without nicotine replacement.

Pregnancy Warning
Tobacco smoke, which has been shown to be harmful to the fetus, contains nicotine, hydrogen cyanide, and carbon monoxide. Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that Habitrol treatment can cause fetal harm when administered to a pregnant woman. The effect of nicotine delivery by Habitrol systems has not been examined in pregnancy (see PRECAUTIONS, Other Effects). Therefore pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches. If Habitrol therapy is used during pregnancy, or if the patient becomes pregnant while using Habitrol treatment, the patient should be apprised of the potential hazard to the fetus.

Safety Note Concerning Children
The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if Habitrol systems are applied or ingested by children or pets. Used 21 mg/day systems contain about 60% (32 mg) of their initial drug content. Therefore, patients should be cautioned to keep both used and unused Habitrol systems out of the reach of children and pets.

PRECAUTIONS
General
The patient should be urged to stop smoking completely when initiating Habitrol therapy (see DOSAGE AND ADMINISTRATION). Patients should be informed that if they continue to smoke while using Habitrol systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the Habitrol dose should be reduced or Habitrol treatment discontinued (see WARNINGS). Physicians should anticipate that concomitant medications may need dosage adjustment (see Drug Interactions).

The use of Habitrol systems beyond 3 months by patients who stop smoking should be discouraged because the chronic consumption of nicotine by any route can be harmful and addicting.

Allergic Reactions: In a 6-week open-label dermal irritation and sensitization study of Habitrol systems, 22 of 220 patients exhibited definite erythema at 24 hours after application. Upon rechallenge, 3 patients exhibited mild-to-moderate contact allergy. Patients with contact sensitization should be cautioned that a serious reaction could occur from exposure to other nicotine-containing products or smoking. In the efficacy trials, erythema following system removal was typically seen in about 17% of patients, some edema in 4%, and dropouts due to skin reactions occurred in 6% of patients.

Patients should be instructed to promptly discontinue the Habitrol treatment and contact their physicians if they experience severe or persistent local skin reactions at the site of application (e.g., severe erythema, pruritus or edema) or a generalized skin reaction (e.g., urticaria, hives, or generalized rash).

Skin Disease: Habitrol systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Cardiovascular or Peripheral Vascular Diseases: The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buerger's disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of Habitrol treatment was reported occasionally. If serious cardiovascular symptoms occur with Habitrol treatment, it should be discontinued.

Habitrol treatment should generally not be used in patients during the immediate post-myocardial infarction period, patients with serious arrhythmias, and patients with severe or worsening angina pectoris.

Renal or Hepatic Insufficiency: The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment. However, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Endocrine Diseases: Habitrol treatment should be used with caution in patients with hyperthyroidism, pheochromocytoma or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease: Nicotine delays healing in peptic ulcer disease; therefore, Habitrol treatment should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Accelerated Hypertension: Nicotine constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Habitrol treatment should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking cessation program outweigh the risks.

Information for Patients
A patient instruction sheet is included in the package of Habitrol systems dispensed to the patient. It contains important information and instructions on how to use and dispose of Habitrol systems properly. Patients should be encouraged to ask questions of the physician and pharmacist.

Patients must be advised to keep both used and unused systems out of the reach of children and pets.

Drug Interactions
Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
Insulin	Increase of subcutaneous insulin absorption with smoking cessation
Adrenergic antagonists (e.g., prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation

May Require an Increase in Dose at Cessation of Smoking	Possible Mechanism
Adrenergic agonists (e.g., isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

Carcinogenesis, Mutagenesis, Impairment of Fertility
Nicotine itself does not appear to be a carcinogen in laboratory animals. However, nicotine and its metabolites increased the incidence of tumors in the cheek pouches of hamsters and forestomach of F344 rats, respectively, when given in combination with tumor-initiators. One study, which could not be replicated, suggested that cotinine, the primary metabolite of nicotine, may cause lymphoreticular sarcoma in the large intestine in rats.

Nicotine and cotinine were not mutagenic in the Ames *Salmonella* test. Nicotine induced repairable DNA damage in an *E. coli* test system. Nicotine was shown to be genotoxic in a test system using Chinese hamster ovary cells. In rats and rabbits, implantation can be delayed or inhibited by a reduction in DNA synthesis that appears to be caused by nicotine. Studies have shown a decrease in litter size in rats treated with nicotine during gestation.

Pregnancy Category D (see WARNINGS)
The harmful effects of cigarette smoking on maternal and fetal health are clearly established. These include low birth weight, an increased risk of spontaneous abortion, and increased perinatal mortality. The specific effects of Habitrol treatment on fetal development are unknown. Therefore, pregnant smokers should be encouraged to attempt cessation using educational and behavioral interventions before using pharmacological approaches.

Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded.

Habitrol treatment should be used during pregnancy only if the likelihood of smoking cessation justifies the potential risk of use of nicotine replacement by the patient, who may continue to smoke.

Teratogenicity
Animal Studies: Nicotine was shown to produce skeletal abnormalities in the offspring of mice when given doses toxic to the dams (25 mg/kg/day IP or SC).

Human Studies: Nicotine teratogenicity has not been studied in humans except as a component of cigarette smoke (each cigarette smoked delivers about 1 mg of nicotine). It has not been possible to conclude whether cigarette smoking is teratogenic to humans.

Other Effects
Animal Studies: A nicotine bolus (up to 2 mg/kg) to pregnant rhesus monkeys caused acidosis, hypercarbia, and hypotension. Fetal and maternal concentrations were about 20 times those achieved after smoking 1 cigarette in 5 minutes). Fetal breathing movements were reduced in the fetal lamb after intravenous injection of 0.25 mg/kg nicotine to the ewe (equivalent to smoking 1 cigarette every 20 seconds for 5 minutes). Uterine blood flow was reduced about 30% after infusion of 0.1 mg/kg/min nicotine for 20 minutes to pregnant rhesus monkeys (equivalent to smoking about six cigarettes every minute for 20 minutes).

Human Experience: Cigarette smoking during pregnancy is associated with an increased risk of spontaneous abortion, low-birth-weight infants and perinatal mortality. Nicotine and carbon monoxide are considered the most likely mediators of these outcomes. The effects of cigarette smoking on fetal cardiovascular parameters has been studied near term. Cigarettes increased fetal aortic blood flow and heart rate, and decreased uterine blood flow and fetal breathing movements. Habitrol treatment has not been studied in pregnant humans.

Labor and Delivery
Habitrol systems are not recommended to be left on during labor and delivery. The effects of nicotine on the mother or the fetus during labor are unknown.

Nursing Mothers
Caution should be exercised when Habitrol therapy is administered to nursing women. The safety of Habitrol treatment in nursing infants has not been examined. Nicotine passes freely into breast milk; the milk-to-plasma ratio averages 2.9. Nicotine is absorbed orally. An infant has the ability to clear nicotine by hepatic first-pass clearance; however, the efficiency of removal is probably lowest at birth. The nicotine concentrations in milk can be expected to be lower with Habitrol treatment when used as directed than with cigarette smoking, as maternal plasma nicotine concentrations are generally reduced with nicotine replacement. The risk of exposure of the infant to nicotine from Habitrol systems should be weighed against the risks associated with the infant's exposure to nicotine from continued smoking by the mother (passive smoke exposure and contamination of breast milk with other components of tobacco smoke) and from Habitrol systems alone or in combination with continued smoking.

Pediatric Use
Habitrol systems are not recommended for use in children because the safety and effectiveness of Habitrol treatment in children and adolescents who smoke have not been evaluated.

Geriatric Use
Forty-eight patients over the age of 60 participated in clinical trials of Habitrol therapy. Habitrol therapy appeared to be as effective in this age group as in younger smokers.

ADVERSE REACTIONS
Assessment of adverse events in the 792 patients who participated in controlled clinical trials is complicated by the occurrence of GI and CNS effects of nicotine withdrawal as well as nicotine excess. The actual incidences of both are confounded by concurrent smoking by many of the patients. In the trials, when reporting adverse events, the investigators did not attempt to identify the cause of the symptom.

Topical Adverse Events
The most common adverse event associated with topical nicotine is a short-lived erythema, pruritus, or burning at the application site, which was seen at least once in 35% of patients on Habitrol treatment in the clinical trials. Local erythema after system removal was noted at least once in 17% of patients and local edema in 4%. Erythema generally resolved within 24 hours. Cutaneous hypersensitivity (contact sensitization) occurred in 2% of patients on Habitrol treatment (see PRECAUTIONS, Allergic Reactions).

Probably Causally Related
The following adverse events were reported more frequently in Habitrol-treated patients than in placebo-treated patients or exhibited a dose response in clinical trials:

Digestive system – Diarrhea,* dyspepsia.*
Mouth/Tooth disorders – Dry mouth.
Musculoskeletal system – Arthralgia,* myalgia.*
Nervous system – Abnormal dreams,† somnolence.†

Frequencies for 21 mg/day system
*Reported in 3% to 9% of patients.
†Reported in 1% to 3% of patients.
Unmarked if reported in < 1% of patients.

Causal Relationship Unknown
Adverse events reported in Habitrol- and placebo-treated patients at about the same frequency in clinical trials are listed below. The clinical significance of the association between Habitrol treatment and these events is unknown, but they are reported as alerting information for the clinician.

Body as a whole – Allergy,† back pain.†
Cardiovascular system – Hypertension.†
Digestive system – Abdominal pain,† constipation,† nausea,* vomiting.
Nervous system – Dizziness,* concentration impaired,† headache (17%), insomnia.*
Respiratory system – Cough increased,† pharyngitis,† sinusitis.†
Urogenital system – Dysmenorrhea.*

Frequencies for 21 mg/day system
*Reported in 3% to 9% of patients.
†Reported in 1% to 3% of patients.
Unmarked if reported in < 1% of patients.

DRUG ABUSE AND DEPENDENCE
Habitrol systems are likely to have a low abuse potential based on differences between it and cigarettes in four characteristics commonly considered important in contributing to abuse: much slower absorption, much smaller fluctuations in blood levels, lower blood levels of nicotine, and less frequent use (i.e., once daily).

Dependence on nicotine polacrilex chewing gum replacement therapy has been reported. Such dependence might also occur from transference to Habitrol systems of tobacco-based nicotine dependence. The use of the system beyond 3 months has not been evaluated and should be discouraged.

To minimize the risk of dependence, patients should be encouraged to withdraw gradually from Habitrol treatment after 4 to 8 weeks of usage. Recommended dose reduction is to progressively decrease the dose every 2 to 4 weeks (see DOSAGE AND ADMINISTRATION).

CAUTION: Federal law prohibits dispensing without prescription.
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CASE REPORTS

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READERS' COMMENTS

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Calibration Using Angiographic Catheters as Scaling Devices — Importance of Filming the Catheters Not Filled with Contrast Medium
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Correction

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